Andrew J. Miller
Alan H. Pollack
BUDD LARNER, P.C.
150 John F. Kennedy Parkway
Short Hills, New Jersey 07078
973-379-4800
Attorneys for Plaintiffs
Dr. Reddy's Laboratories, Ltd., and
Dr. Reddy's Laboratories, Inc.

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

DR. REDDY'S LABORATORIES, LTD., and DR. REDDY'S LABORATORIES, INC., Plaintiffs, v. ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, and MERCK & CO., INC Defendants	Civil Action No. __________

DR. REDDY'S LABORATORIES, LTD.'S AND
DR. REDDY'S LABORATORIES, INC.'S
COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiffs Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (collectively, "DRL") for their Complaint against AstraZeneca AB, Aktiebolaget Hässle, AstraZeneca LP (collectively, "AstraZeneca"), and Merck & Co., Inc. ("Merck") allege and aver as follows:

PARTIES

1. Plaintiff Dr. Reddy's Laboratories, Ltd. is an Indian corporation, with its principal place of business at 7-1-27, Ameerpet, Hyderabad, India.

2. Plaintiff Dr. Reddy's Laboratories, Inc. is a New Jersey corporation, with its principal place of business at 200 Somerset Corporate Boulevard, Bridgewater, New Jersey.

3. On information and belief, Defendant AstraZeneca AB is a Swedish company, with its principal place of business at Södertälje, Sweden.

4. On information and belief, Defendant Aktiebolaget Hässle is a Swedish company, with its principal place of business at Mölndal, Sweden.

5. On information and belief, Defendant AstraZeneca L.P. is a Delaware limited partnership, with its principal place of business at Wilmington, Delaware.

6. On information and belief, Defendant Merck & Co., Inc. is a New Jersey corporation, with its principal place of business at Whitehouse Station, New Jersey.

JURISDICTION AND VENUE

7. This is an action for declaratory judgment pursuant to the Federal Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, together with such further and other relief that may be necessary or proper. The basis for declaratory judgment is an actual controversy between DRL and Defendants AstraZeneca and Merck arising under the United States Patent Laws, Title 35 of the United States Code. This Court has subject matter jurisdiction over the action based on 28 U.S.C. §§ 1331 and 1338.

8. This Court has personal jurisdiction over AstraZeneca because of its continuous and systematic contacts with the State of New Jersey, including its conducting

of substantial and regular business therein through the marketing and sales of its pharmaceutical products in New Jersey.

9. This Court has personal jurisdiction over Merck because of its continuous and systematic contacts with the State of New Jersey, including is maintaining a principal place of business in this District.

10. Venue is proper in this judicial district pursuant to 28 U.S.C. § 1391(b) and (c) and/or 1400(b).

BACKGROUND

11. On information and belief, AstraZeneca or an affiliated entity is the owner of approved New Drug Application ("NDA") No. 21-153 for esomeprazole magnesium in capsule form, 20 mg and 40 mg.

12. On information and belief, AstraZeneca, by themselves or through affiliated entities, market NEXIUM® esomeprazole magnesium 20 mg and 40 mg capsules throughout the United States under NDA No. 21-153.

13. AstraZeneca has informed the United States Food and Drug Administration ("FDA") of the following unexpired patents "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of [esomeprazole magnesium capsules]": U.S. Patent Nos. 4,738,974 ("the '974 patent"), 4,786,505 ("the '505 patent), 4,853,230 ("the '230 patent"), 5,690,960 ("the '960 patent"), 5,714,504 ("the '504 patent"), 5,877,192 ("the '192 patent"), 5,900,424 ("the '424 patent"), 6,147,103 ("the '103 patent"), 6,166,213 ("the '213 patent"), 6,191,148 ("the'148 patent"), 6,369,085 ("the '085 patent"), 6,428,810 ("the '810 patent"), and 6,875,872 ("the '872 patent"),. *See* 21

U.S.C. § 355(b)(1), (c)(2). The FDA listed these patents in a publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the "Orange Book," in connection with NDA No. 21-153. *See* 21 U.S.C. § 355(j)(2)(A)(i).

14. Upon FDA approval of DRL's Esomeprazole Magnesium Delayed Release Capsules (equivalent to 20 mg and 40 mg of omeprazole free base), DRL intends to market this product in the United States after the expiration of the '974, '505, and '230 patents. DRL seeks to market its Esomeprazole Magnesium Delayed Release Capsules before the expiration of the '960, '504, '192, '424, '103, '213, '148, '085, '810 and '872 patents, and filed a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "Paragraph IV certification") certifying that these patents are either invalid or will not be infringed by the manufacture, use or sale of DRL's proposed Esomeprazole Magnesium Delayed Release Capsules.

15. In connection with the filing of its Paragraph IV certification, DRL provided Defendants with an offer of confidential access to its ANDA in accordance with 21 U.S.C. §§ 355(j)(5)(C)(i)(I)(cc) and (III).

THE CONTROVERSY

16. On information and belief, AstraZeneca owns the '960 patent, entitled "Pharmaceutical Formulation of Omeprazole," a copy of which is attached hereto as Exhibit A.

17. On information and belief, AstraZeneca owns the '424 patent, entitled "Omeprazole Magnesium Salt Form," a copy of which is attached hereto as Exhibit B.

18. On information and belief, AstraZeneca owns the '103 patent, entitled "Omeprazole Process and Compositions Thereof," a copy of which is attached hereto as Exhibit C.

19. On information and belief, Merck owns the '213 patent, entitled "Omeprazole Process and Compositions Thereof," a copy of which is attached hereto as Exhibit D.

20. On information and belief, Merck owns the '148 patent, entitled "Omeprazole Process and Compositions Thereof," a copy of which is attached hereto as Exhibit E.

21. On information and belief, AstraZeneca owns the '810 patent, entitled "Pharmaceutical Formulation Comprising Omeprazole," a copy of which is attached hereto as Exhibit F.

22. On January 17, 2008, AstraZeneca sued DRL, alleging, *inter alia*, infringement of the '504, '872, and '085 patents; it did not allege infringement of the '960, '192, '424, '103, '213, '148 and '810 patents. *See AstraZeneca AB, et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 08-(D.N.J). The 45-day period following Defendants' receipt of DRL's notice of Paragraph IV certification has expired.

23. Because Defendants did not assert the '960, '424, '103, '213, '148 and '810 patents within the 45 days following receipt of DRL's notice of Paragraph IV certification, DRL faces uncertainty and great potential risk if AstraZeneca should assert any of the '960, '424, 103, '213, '148 and '810 patents after DRL begins commercially marketing its Esomeprazole Magnesium Delayed Release Capsules.

24. Accordingly, there is an actual, substantial, and continuing justiciable case and controversy between DRL and Defendants AstraZeneca and Merck regarding the validity and infringement of the '960, '424, '103, '213,'148 and '810 patents, over which this Court can and should exercise jurisdiction and declare the rights of the parties. DRL is therefore entitled to bring and maintain this action for declaratory judgment. 21 U.S.C. § 355(j)(5)(C).

COUNT I
DECLARATORY JUDGMENT OF NONINFRINGEMENT

25. DRL's commercial manufacture, use, offer for sale, sale or importation of its generic equivalents of Nexium® or the active ingredient thereof would not infringe the '960 patent.

COUNT II
DECLARATORY JUDGMENT OF NONINFRINGEMENT

26. DRL's commercial manufacture, use, offer for sale, sale or importation of its generic equivalents of Nexium® or the active ingredient thereof would not infringe the '424 patent.

COUNT III
DECLARATORY JUDGMENT OF NONINFRINGEMENT

27. DRL's commercial manufacture, use, offer for sale, sale or importation of its generic equivalents of Nexium® or the active ingredient thereof would not infringe the '103 patent.

COUNT IV
DECLARATORY JUDGMENT OF NONINFRINGEMENT

28. DRL's commercial manufacture, use, offer for sale, sale or importation of its generic equivalents of Nexium® or the active ingredient thereof would not infringe the '213 patent.

COUNT V
DECLARATORY JUDGMENT OF NONINFRINGEMENT

29. DRL's commercial manufacture, use, offer for sale, sale or importation of its generic equivalents of Nexium® or the active ingredient thereof would not infringe the '148 patent.

COUNT VI
DECLARATORY JUDGMENT OF NONINFRINGEMENT

30. DRL's commercial manufacture, use, offer for sale, sale or importation of its generic equivalents of Nexium® or the active ingredient thereof would not infringe the '810 patent.

PRAYER FOR RELIEF

WHEREFORE, DRL respectfully requests the Court enter judgment against AstraZeneca and Merck to include:

A. a declaration that DRL's manufacture, use or sale of its generic equivalents of Nexium® or the active ingredient thereof will not infringe United States Patent No. 5,690,960;

B. a declaration that DRL's manufacture, use or sale of its generic equivalents of Nexium® or the active ingredient thereof will not infringe United States Patent No. 5,900,424;

C. a declaration that DRL's manufacture, use or sale of its generic equivalents of Nexium® or the active ingredient thereof will not infringe United States Patent No. 6,147,103;

D. a declaration that DRL's manufacture, use or sale of its generic equivalents of Nexium® or the active ingredient thereof will not infringe United States Patent No. 6,166,213;

E. a declaration that DRL's manufacture, use or sale of its generic equivalents of Nexium® or the active ingredient thereof will not infringe United States Patent No. 6,191,148;

F. a declaration that DRL's manufacture, use or sale of its generic equivalents of Nexium® or the active ingredient thereof will not infringe United States Patent No. 6,428,810;

G. an award of DRL's reasonable costs and attorneys' fees in connection with this action; and

H. all such other and further relief as the Court may deem just and proper.

Respectfully submitted,
BUDD LARNER, P.C.

Dated: May 19, 2008

By: s/ Alan H. Pollack

Alan H. Pollack
150 John F. Kennedy Parkway
Short Hills, New Jersey 07078
Attorneys Plaintiffs
Dr. Reddy's Laboratories, Ltd., and
Dr. Reddy's Laboratories, Inc.

LOCAL CIVIL RULE 11.2 CERTIFICATION

Plaintiffs, by its attorneys, hereby certify that to the best of its knowledge the specific matters in controversy herein are not the subject of any action pending in any court, or of any pending arbitration or administrative proceeding. Plaintiffs provide notice of pendency in this District of actions related to this case as follows. Specifically, the following cases relate to claims of patent infringement arising out of Abbreviated New Drug Applications concerning generic esomeprazole magnesium capsules, the product at issue in this action: *AstraZeneca AB, et al v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 08-CV-00328-JAP-TJB; *Ivax Pharmaceuticals, Inc. v., AstraZeneca AB, et al.* Civil Action No. 08-CV-02165-JAP-TJB; and *AstraZeneca AB, et al v. Ivax Corporation., et al.*, original Civil Action No. 06-CV-01057-JAP-TJB, consolidated with Civil Action No. 05-CV-05553-JAP-TJB.

I hereby certify that the following statements made by me are true. I am aware that if any of the foregoing statements made by me are willfully false, I am subject to punishment.

Dated: May 19, 2008

s/ Alan H. Pollack
Alan H. Pollack

EXHIBIT A

US005690960A

United States Patent [19]

Bengtsson et al.

[11] **Patent Number: 5,690,960**

[45] **Date of Patent: Nov. 25, 1997**

[54] **PHARMACEUTICAL FORMULATION OF OMEPRAZOLE**

[75] Inventors: **Inga Siv Bengtsson**, Göteborg; **Kurt Ingmar Lövgren**, Mölnlycke, both of Sweden

[73] Assignee: **Astra Aktiebolag**, Sodertalje, Sweden

[21] Appl. No.: **313,036**

[22] PCT Filed: **Jul. 8, 1994**

[86] PCT No.: **PCT/SE94/00681**

§ 371 Date: **Sep. 27, 1994**

§ 102(e) Date: **Sep. 27, 1994**

[87] PCT Pub. No.: **WO95/01783**

PCT Pub. Date: **Jan. 19, 1995**

[30] **Foreign Application Priority Data**

Jul. 9, 1993 [SE] Sweden 9302395

[51] **Int. Cl.**^{6} **A61K 9/32**; A61K 9/36

[52] **U.S. Cl.** **424/480**; 424/474; 424/482; 424/494; 424/497

[58] **Field of Search** 424/480, 474, 424/482, 494, 497

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,738,974	4/1988	Brandstrom	514/338
4,786,505	11/1988	Lovgren et al.	424/468

FOREIGN PATENT DOCUMENTS

0005129	4/1981	European Pat. Off. .
0124495	11/1984	European Pat. Off. .
0342522	11/1989	European Pat. Off. .
0247983	12/1990	European Pat. Off. .
9501783	8/1994	WIPO .

OTHER PUBLICATIONS

Pilbrant et al., "Development of an oral formulation of omeprazole," Scand J Gastroenterol 1985; vol. 20 (Suppl 108) : 113–120.

Primary Examiner—Thurman K. Page
Assistant Examiner—James M. Spear
Attorney, Agent, or Firm—White & Case

[57] **ABSTRACT**

A new oral pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole, a method for the manufacture of such a formulation, and the use of such a formulation in medicine.

22 Claims, No Drawings

PHARMACEUTICAL FORMULATION OF OMEPRAZOLE

This application is a 371 of PCT/SE 94/00681 filed Jul. 8, 1994.

FIELD OF THE INVENTION

The present invention is related to a new pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole, to a method for the manufacture of such a formulation, and to the use of such a formulation in medicine.

BACKGROUND OF THE INVENTION

The compound known under the generic name omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, is described i.a. in EP-A 0 005 129.

Omeprazole is useful for inhibiting gastric acid secretion and has gastric mucosa protective activity. In a more general sense, omeprazole may be used for prevention and treatment of gastric acid related disorders in mammals and man, including e.g. gastroesofageal reflux disease, gastritis, gastric ulcer and duodenal ulcer. Omeprazole is susceptible to degradation/transformation in acid reacting and neutral media. The half-life of degradation of omeprazole in water solutions at pH-values less than four is shorter than ten minutes. Also at neutral pH-values degradation proceeds rapidly, e.g. at pH=7 the half-life of omeprazole is about 14 hours, while at higher pH-values the stability in solution is much better (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113–120). Omeprazole also in the solid state is susceptible to degradation and is stabilized in mixtures with alkaline reacting compounds. The stability of omeprazole is also affected by moisture, heat, organic solvents and to some degree by light.

From what is said about the stability properties of omeprazole, it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption of omeprazole can occur.

A pharmaceutical oral solid dosage form of omeprazole must be protected from contact with acidic gastric juice by an enteric coating. In U.S. Pat. No. 4,786,505 is described an enteric coated omeprazole preparation containing a separating subcoat between the core material and the enteric coating. Said preparation contains an alkaline core comprising omeprazole, a subcoating and an enteric coating.

Certain salts of omeprazole including alkaline reacting salts of omeprazole are described in EP-A 0 124 495. In said patent specification the requirements and importance regarding storage stability of omeprazole for incorporation in pharmaceutical preparations are emphasized.

There is however, a demand for the development of new enteric preparations of omeprazole with enhanced stability and for environmental aspects there is also a strong desire for the use of water based processes in production of pharmaceutical products.

The isolation and purification in full manufacturing scale of the magnesium omeprazole salts described in EP-A 0 124 495 presents one major problem in that the magnesium omeprazole salt particles are very fragile making pharmaceutical manufacturing processes utilising this product less

attractive in full scale production. Performing the process without crystallization of the magnesium omeprazole gives a product which is less suitable as a pharmaceutical substance.

In order to use the magnesium salt of omeprazole, in this specification denoted magnesium omeprazole, in full manufacturing scale in preparing pharmaceutical formulations primarily for oral administration, such as tablets, it is necessary that said magnesium omeprazole possesses a combination of properties which makes such full scale manufacturing feasible.

The combination of physical properties of the novel magnesium omeprazole product described in the present specification with respect to the degree of crystallinity, particle diameter, density, hygroscopicity, low water content and low content of other solvents is favorable and permits the manufacture of magnesium omeprazole in a form which is useful for the manufacture of the new pharmaceutical formulation.

The novel form of magnesium omeprazole can be formulated into different dosage forms for oral and rectal administration. Examples of such formulations are tablets, granules, pellets, capsules, suppositories and suspensions.

SUMMARY OF THE INVENTION

One object of the present invention is to provide a pharmaceutical formulation of magnesium omeprazole.

Another object of the present invention is to provide a process for full scale production of pharmaceutical formulations of omeprazole, especially an enteric coated dosage form of omeprazole, which is resistant to dissolution in acid media and which dissolves rapidly in neutral to alkaline media and has a good stability during long-term storage.

Yet another object of the invention is to provide an environment friendly completely water-based process for the manufacture of pharmaceutical formulations of omeprazole.

The new dosage form is characterized in the following way. Core material in the form of pellets, granules or tablets containing the novel form of a magnesium salt of omeprazole, optionally together with an alkaline reacting compound, and on said core material one or more subcoating layers optionally comprising tablet excipients which are soluble or insoluble but disintegrating in water, or polymeric, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the core and an outer layer, which is an enteric coating. This/these inner layer/layers separates/separate the core material from the outer layer being an enteric coating.

The process of forming the enteric coated dosage form is preferably water-based. Also the enteric coating process step, which usally is carried out using an organic solvent, can be carried out using a water-based process which is desirable both for the working environment inside the pharmaceutical plant and for global environmental reasons.

It has been found that a magnesium omeprazole having a degree of crystallinity which is higher than 70% is useful in the manufacture of the pharmaceutical formulations of omeprazole according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The new pharmaceutical formulation is defined in claims **1–8**, a process for the manufacture of the pharmaceutical formulation according to the present invention is defined in claims **9–10** and the use of the formulation in medicine is defined in claims 11–17.

Magnesium Omeprazole

Magnesium omeprazole feasible for the manufacturing of the claimed formulation has the following properties:

a) Crystalline form, with a degree of crystallinity of not less than 70%, preferably higher than 75% as determined by X-ray powder diffraction

It is desirable that the product also exhibits the following properties;

b) Particle size measured as mean mass diameter (MMD) less than 30 μm, preferably less than 20 μm as determined by laser diffraction technique.

c) Density between 1.33 g/cm^3 and 1.35 g/cm^3 as determined by powder pycnometer.

d) Hygroscopicity not exceeding 2% increase of weight upon storage for one month up to 94% relative atmospheric humidity as determined gravimetrically.

e) A content of water of between 5% and 10% by weight as determined by titration according to Karl Fischer.

f) A content of methanol less than 0.1% preferably less than 0.05% by weight as determined by gas chromatography, in case methanol is used as solvent.

The process for producing the novel form of magnesium omeprazole is characterized by the following consecutive steps

1) treating omeprazole or a salt thereof with magnesium alcoholate in a solution
2) separating inorganic salts from the reaction mixture
3) crystallizing magnesium omeprazole
4) isolating the obtained crystalline magnesium omeprazole and, optionally
5) purifying and drying the crystalline magnesium omeprazole using conventional methods.

The process for manufacturing the novel magnesium omeprazole can be described in the following way:

A lower alcohol, such as methanol, ethanol, n-propanol or iso-propanol, preferably methanol, is treated in a solution of polar solvents with a weighed amount of magnesium at temperatures between 0° C. and reflux temperature. The temperature should preferably be between 10° and 30° C. After addition of the magnesium to the solution the temperature can, in a second step be raised further to between 0° C. and reflux temperature, preferably 20°–50° C. After termination of the reaction the temperature is reduced to 0°–40° C., preferably 10°–25° C. Omeprazole or a salt of omeprazole is then added to the solution and after termination of the reaction the mixture is cooled to −10° C. to +20° C., preferably −5° C. to +5° C. The solvent is then evaporated to 40–60% of the initial volume, which makes the inorganic salts precipitate. The precipitate is separated from the reaction solution for example by centrifugation or filtration and the solution is heated to 5° C. to 30° C. whereafter the solution is seeded with magnesium omeprazole crystals. An amount of water, which is approximately equal to the volume of the solution, is added to start the crystallization. The solution is cooled to −10°to +20° C., preferably 0°–10° C. to complete the crystallization. The crystals are then separated from the mother liquid for example by centrifugation or filtration and washed with polar solvents preferably an aqueous lower alcohol such as aqueous methanol. Finally, the crystals are dried preferably under reduced pressure and heating.

Pharmaceutical formulations containing the novel magnesium omeprazole described above are manufactured as described herein below.

Core Material

The novel magnesium salt of omeprazole, herein referred to as magnesium omeprazole, is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of omeprazole in the final mixture. Optionally the magnesium omeprazole may be mixed with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

The powder mixture is then formulated into pellets, granules or tablets, by conventional pharmaceutical procedures. The pellets, granules or tablets are used as core material for further processing.

Separating Layer—Subcoating

The cores containing magnesium omeprazole and optionally alkaline reacting substances are separated from the enteric coating polymer(s). The subcoating layer, in the following defined as the separating layer, serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the core can react with hydroxyl ions diffusing from the core towards the surface of the coated particles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids or salts thereof.

The separating layer may consist of one or more layers.

The separating layer(s) can be applied to the core material—pellets, granules or tablets—by conventional coating procedures in a suitable coating pan, centrifugal fluidized coating-granulator, or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among pharmaceutically acceptable, inert compounds or polymers used for film-coating applications such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxymethyl cellulose or hydroxypropyl methylcellulose. The separating layer, "subcoating", applied to the core material may constitute from approximately 0.5 to 25% by weight of the core weight, preferably 2.0–10.0%, and more preferably 2.5–5.0%.

In the case of a tablet formulation another method to apply the separating layer(s) can be performed by drycoating technique. First a tablet containing magnesium omeprazole is formulated as described above. Around this tablet one or more layers are compressed using a suitable tableting machine. The separating layer(s) consists of pharmaceutically acceptable, soluble or insoluble but in water disintegrating tablet excipients. The separating layer(s) has preferably a thickness of not less than approximately 1 mm.

Ordinary plasticizers, colorants, pigments, titanium dioxide, talc and other additives may also be included into one or more of the separating layer(s).

Enteric Coating Layer

The enteric coating layer is applied in one or more layers onto the subcoated core material by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water, or by using latex suspensions of said polymers or optionally using polymer solutions in suitable organic solvents. As enteric coating polymers can be used one or more of the following, for example solutions or dispersions of acrylates (methacrylic acid/methacrylic acid methylester copolymer), cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s). Preferably water-based polymer dispersions such as for example compounds known under the trade names Aquateric® (FMC Corporation), Eudragit® (Röhm Pharma), Aqoat™ (Shin-Etsu Chemical), Opadry™ (Colorcon) or similar compounds are used to obtain enteric coatings. The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer for example cetanol, triacetin, citric acid esters such as, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate, polyethylene glycol (PEG) or similar plasticizers. The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1–50% of the enteric coating polymer(s). Dispersants such as talc, colorants and pigments may also be included into the enteric coating layer or sprayed onto the enteric coated material as an overcoat.

The thickness of the enteric coating may vary widely without influencing the in vitro release of omeprazole in test solutions which mimic in vivo conditions in man. To protect the acid susceptible omeprazole compound and to obtain an acceptable acid resistance, the enteric coating constitutes at least an amount of 1.0% by weight of the core weight, preferably at least 3.0% and especially at least 6.0%. The upper amount of the applied enteric coating is normally only limited by processing conditions. This possibility to vary the thickness of the enteric coating without deleterious influence on the release of omeprazole is especially desirable in large scale processes. The enteric coating layer(s) may be applied on the pre-processed formulation containing subcoating layer(s) without exactly controlling the thickness of the applied coating layer(s).

Thus, the formulation according to the invention consists of core material containing magnesium omeprazole optionally mixed with alkaline reacting compound(s). The addition of alkaline reacting material is not necessary, in any sense, but such a substance may further enhance the stability of omeprazole. The core material is coated with an enteric coating rendering the dosage form insoluble in acid media, but disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted. The core material is further coated with an soluble or insoluble but in water disintegrating coating, optionally containing one or more pH-buffering substances, which separate the core material from the enteric coating.

Final Dosage Form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets or granules, these pellets or granules dispensed in hard gelatin capsules or sachets. The final dosage form may further be coated with an additional layer containing pigment(s) and/or colorant(s). It is essential for the long term stability during storage that the water content of the final dosage form containing magnesium omeprazole (enteric coated tablets, capsules, granules or pellets) is kept low.

Process

A process for the manufacture of a dosage form according to the present invention represents a further aspect of the invention. After the forming of the core material, said material is first coated with the separating layer(s) and then with the enteric coating layer(s). The coating(s) are carried out as described above. Further another aspect of the invention is that the pharmaceutical processes can be completely water-based.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and the disease. In general the daily dose will be in the range of 1–400 mg of omeprazole.

The invention is illustrated in detail by the following examples. Example 1 discloses the preparation of the novel magnesium omeprazole product, which product is suitable in manufacturing of the pharmaceutical formulations according to the present invention. Example 2 discloses compositions of different enteric coated tablets containing magnesium omeprazole and results from acid resistance test and in vitro dissolution test. Examples 3 discloses tablet formulations with different thickness of the enteric coating, the obtained gastric acid resistance of said formulations and the in vitro release rate of omeprazole. Example 4 discloses an enteric coated pellet formulation.

EXAMPLES

The following detailed Example 1 will serve to illustrate a process for manufacturing the magnesium omeprazole, which will be used in the pharmaceutical preparations according to the present invention.

Example 1

A reactor was filled with 2026 liters of methanol. The stirrer was started and the temperature was adjusted to 20° C. 3,90 kg of magnesium was added to the vessel and immediately thereafter 1,0 liter of CH_2Cl_2. The reactor was heated to 40° C. and kept at this temperature for 60 min. It was then cooled to 15° C. before the addition of 99,9 kg of omeprazole. The reactor was kept at this temperature for 60 min and then cooled to 0° C. The temperature was kept at this level for 30 minutes before 1000 L of methanol were evaporated under vacuum and the inorganic solid salt was separated from the liquid first by centrifugation and then by filtration. The liquid was heated to 10° C. and the liquid was seeded with magnesium omeprazole crystals whereafter the magnesium omeprazole salt was precipitated by addition of 900 L of water. The mixture was then cooled to 5° C. After the crystallization had been completed the magnesium omeprazole crystals were centrifuged off and then washed with a mixture of 50 L of methanol and 150 L of water. The produced magnesium omeprazole was dried under reduced pressure finally producing 92,5 kg of crystalline product corresponding to a yield of 81,4%.

The novel form of the magnesium salt of omeprazole according to Example 1 fulfills the properties defined above.

Example 2

Tablet formulations containing magnesium omeprazole.

Amount omeprazole Ingredient	10 (mg/tabl)	20 (mg/tabl)	40 (mg/tabl)
Tablet core			
Magnesium omeprazole	11.2	22.5	45.0
Mannitol	68.7	57.4	34.9
Microcrystalline cellulose	25.0	25.0	25.0
Sodium starch glycolate	6.0	6.0	6.0
Hydroxypropyl methylcellulose	6.0	6.0	6.0
Talc	5.0	5.0	5.0
Sodium stearyl fumarate	2.5	2.5	2.5
Water purified	50.0	50.0	50.0
Sub-coating layer			
Hydroxypropyl methylcellulose	3.7	3.7	3.7
Hydrogen peroxide 30%	0.04	0.04	0.04
Water purified	34.0	34.0	34.0
Enteric coating layer			
Methacrylic acid copolymer	9.1	9.1	9.1
Polyethylene glycol	1.0	1.0	1.0
Titanium dioxide	0.82	1.1	0.51
Colour iron oxide, red-brown	0.04	0.13	0.43
Colour iron oxide, yellow	0.02	—	—
Water purified	45.0	45.0	45.0
Polish			
Paraffin powder	0.05	0.05	0.05

The tablets with an amount of 20 mg omeprazole/tablet have been manufactured both in a pilot scale of about 300 000 tablets and a large scale of about 2 million tablets.

Description of Manufacturing

Magnesium omeprazole, mannitol, hydroxypropyl methylcellulose, microcrystalline cellulose and sodium starch glycolate are dry-mixed, moistened with water and wet mixed. The wet mass is dried and milled and finally mixed with anti-adherent and lubricant substances. The milled granulate is compressed to tablets with a diameter of 7 mm. The tablets are sub-coated with a polymer film based on hydroxypropyl methylcellulose and enteric coated with a methacrylic acid copolymer film. Water used in the manufacture of the tablets is removed during subsequent processing.

Investigation of Acid-Resistance

Six individual tablets were exposed to artificial gastric fluid without enzymes, pH 1.2. After six hours the tablets were removed, washed and analysed for omeprazole content using HPLC. The amount of omeprazole is taken as acid resistance.

Tablet Strength (mg)	Acid resistance (%)
10	95 (93–98)
20	100 (94–102)
40	100 (96–103)

Investigation of In-Vitro Dissolution

After exposure to acid environment, pH 1.2, as described above, the medium was switched to artificial intestinal fluid without enzymes, pH 6.8. The dissolved amount of omeprazole was determined by HPLC.

Tablet	Dissolved amount of omeprazole (%) after (minutes)						
Strength (mg)	0 (%)	5 (%)	10 (%)	15 (%)	20 (%)	25 (%)	30 (%)
10	0	2	78	92	93	94	94
20	0	0	75	93	96	96	97
40	0	9	71	86	91	91	94

All values of dissolved amount of omeprazole are mean values of 12 tablets.

Example 3

Tablet formulations containing magnesium omeprazole with different thickness of the enteric coating.

The composition of the tablets is the same as in Example 2 (20 mg omeprazole). The tablets (n=6) have been exposed in an artificial gastric juice (pH 1.2) during 2 hours and then analysed for remaining amount of omeprazole (acid resistance). The release of omeprazole was analysed on tablets (n=6) pre-exposed in gastric juice 2 hrs and thereafter exposed in a buffer solution (pH 6.8) during 30 min.

Experiment*)	Enteric coating (% weight per tablet)	Acid resistance (% residue after 2 h; pH 1.2)	Release (% after 30 min; pH 6.8)
A	8	101 (98–105)	94 (93–96)
B	8	100 (98–102)	95 (85–98)
C	16		98 (96–100)

*)A manufactured in large scale
B manufactured in pilot scale
C manufactured in laboratory scale

Example 4

Enteric coated pellet formulation containing magnesium omeprazole.

Pellet core		
Magnesium omeprazole	225	g
Mannitol	1425	g
Hydroxypropyl cellulose	60	g
Microcrystalline cellulose	40	g
Lactose anhydrous	80	g
Sodium lauryl sulphate	5	g

-continued

Disodium hydrogen phosphate dihydrate	8 g
Water purified	350 g
Subcoating layer (I)	
Hydroxypropyl methylcellulose	70 g
Water purified	1450 g
Enteric-coating layer (II)	
Methacrylic acid copolymer	430 g
Polyethylene glycol	40 g
Water purified	1890 g
Polish	
Magnesium stearate	5 g

The dry ingredients given above were mixed well in a mixer. Addition of granulation liquid was made and the mixture was kneaded and granulated to a proper consistency. The wet mass was pressed through an extruder and the granules were converted to spherical form in a spheronizer. The pellets were dried and classified into suitable particle size ranges, e.g. 0.5–1.5 mm.

The polymer solution (I) was sprayed on the uncoated pellets in a fluidized bed apparatus under conditions suitable for the equipment used.

The polymer dispersion (II) was sprayed on the subcoated pellets in a fluidized bed apparatus. The enteric-coated pellets were classified, polishing material was admixed and the pellets were filed into hard gelatin capsules in an amount corresponding to 20 mg of omeprazole, using a capsule filling machine.

Biopharmaceutical Tests

The enteric coated formulations according to Example 2 have been tested in humans with good results.

We claim:

1. A stable oral formulation comprising:

a core containing a magnesium salt of omeprazole said salt having more than 70% crystallinity as determined by x-ray powder diffraction;

a subcoating layer; and

an enteric coating layer, whereby the thickness of the enteric coating layer does not effect the release of omeprazole into solution at the pH predominantly present in the small intestine.

2. A formulation according to claim 1, wherein the formulation is a tablet formulation.

3. A formulation according to claim 1, wherein the formulation is a pellet formulation.

4. A formulation according to claim 1, wherein the enteric coating comprising an enteric coating material, optionally containing one or more pharmaceutically acceptable plasticizers, dispersants, colorants and pigments.

5. A formulation according to claim 4, wherein the enteric coating comprises water-based polymer solutions or dispersions of acrylates, hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, cellulose acetate trimellitate and/or cellulose acetate phthalate.

6. A formulation according to claim 1, wherein the enteric coating constitutes from 1.0% by weight of the weight of the core material.

7. A formulation according to claim 6, wherein the enteric coating constitutes at least 3.0% by weight of the weight of the core material.

8. A formulation according to claim 1 wherein the subcoating layer(s) comprise polymeric, filmforming compounds or tablet excipients which are soluble or insoluble but disintegrating in water, and optionally containing pH-buffering, alkaline compounds.

9. A formulation according to claim 1 wherein the produced enteric coated formulation contains an overcoat, optionally comprising one or more pharmaceutically acceptable plasticizers, dispersants, colorants and pigments.

10. A process for the manufacture of a formulation of a pharmaceutical composition for the oral administration of magnesium omeprazole comprising the steps of:

(a) forming a core material containing magnesium omeprazole salt said salt having at least 70% crystallinity as determined by x-ray powder diffraction;

(b) applying in the presence of water at least one subcoating layer onto the core;

(c) further applying in the pittance of water at least one enteric coating layer onto the subcoated core; and drying the prepared formulation.

11. A process according to claim 10, wherein the subcoating layer(s) is applied on the core material by a dry-coating process.

12. The oral formulation according to claim 8 or 1 wherein the core is coated with more than one subcoating layer.

13. The oral formulation according to any one of the claim 1, 4–7 or 9 wherein the enteric coating comprises more than one layer.

14. The oral formulation according to claim 1 wherein the crystalline magnesium omeprazole has a mean mass particle size diameter of less than 30 μm.

15. The oral formulation according to claim 1 wherein the crystalline magnesium omeprazole has a hygroscopicity of less than 2% by weight.

16. The formulation according to claim 1, wherein the core material is in the form of pellets, granules or tablets.

17. A method for inhibiting gastric acid secretion in mammals and man by administering to a host in need thereof a therapeutically effective dose of an enteric coated formulation according to any of claims 1 to 9.

18. A method for the treatment of gastric acid related diseases in mammals and man by administering to a host in need thereof a therapeutically effective dose of an enteric coated formulation according to any of claims 1 to 9.

19. The formulation according to claim 1, wherein the core further comprises an alkaline reacting compound.

20. The process according to claim 10, wherein the core material further comprises an alkaline reacting compound.

21. A pharmaceutical composition produced in accordance with the process of claim 10.

22. An improved oral pharmaceutical composition containing a core of omeprazole salt with a subcoating and an enteric coating wherein the improvement comprises magnesium omeprazole salt having more than 70% crystallinity as determined by x-ray powder diffraction.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,690,960

DATED : November 25, 1997

INVENTOR(S) : Bengtsson et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

col. 9, line 43 (claim 1, line 7), change "effect" to --significantly affect--;

col. 10, line 22, change "pittance" to --presence--;

col. 10, lines 31, change "claim" to --claims--.

Signed and Sealed this

Second Day of June, 1998

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

E X H I B I T B

US005900424A

United States Patent [19]

Källström et al.

[11] **Patent Number:** **5,900,424**

[45] **Date of Patent:** **May 4, 1999**

[54] **OMEPRAZOLE MAGNESIUM SALT FORM**

[75] Inventors: **Lars Åke Källström**; **Monica Annelie Nygren**, both of Södertälje, Sweden

[73] Assignee: **Astra Aktiebolag**, Sodertalje, Sweden

[21] Appl. No.: **08/313,342**

[22] PCT Filed: **Jul. 8, 1994**

[86] PCT No.: **PCT/SE94/00680**

§ 371 Date: **Sep. 27, 1994**

§ 102(e) Date: **Sep. 27, 1994**

[87] PCT Pub. No.: **WO95/01977**

PCT Pub. Date: **Jan. 19, 1995**

[30] **Foreign Application Priority Data**

Jul. 9, 1993 [SE] Sweden 9302396

[51] **Int. Cl.**[6] **C07D 401/12**; A61K 31/44

[52] **U.S. Cl.** **514/338**; 546/273.7

[58] **Field of Search** 546/273.7; 514/338

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

0005129	4/1981	European Pat. Off. .
0124495	1/1987	European Pat. Off. .
4035455	11/1990	Germany .
9501977	7/1994	WIPO .

OTHER PUBLICATIONS

Drug Development and Industrial Pharmacy, 19(6), 631–641, Labhasetwar et al., 1993.

Kohl et al. CA 117:90285, 1992.

Primary Examiner—Jane Fan
Attorney, Agent, or Firm—White & Case L.L.P.

[57] **ABSTRACT**

A novel compound form of magnesium omeprazole useful in the manufacture of pharmaceutical formulations, the use of the product and the process for its production are described.

22 Claims, 1 Drawing Sheet

Fig. 1

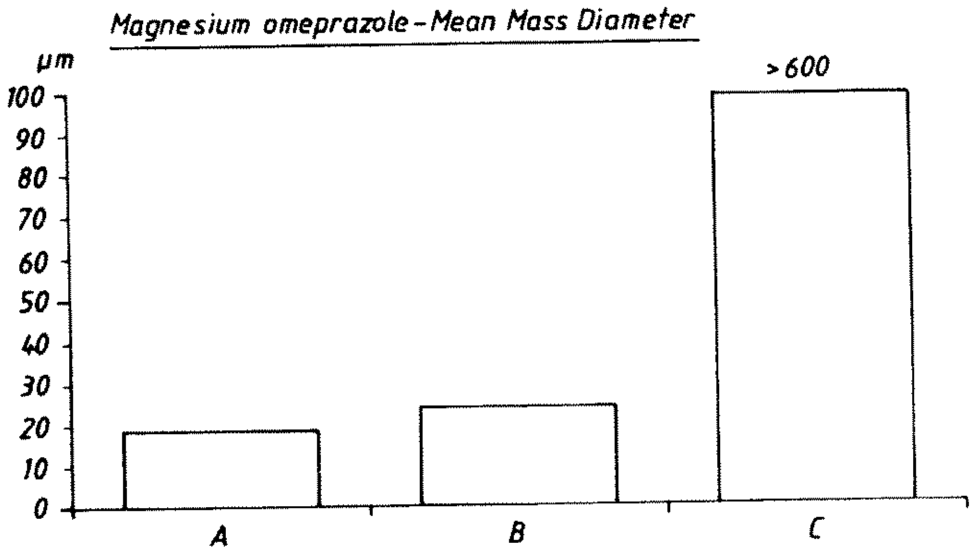
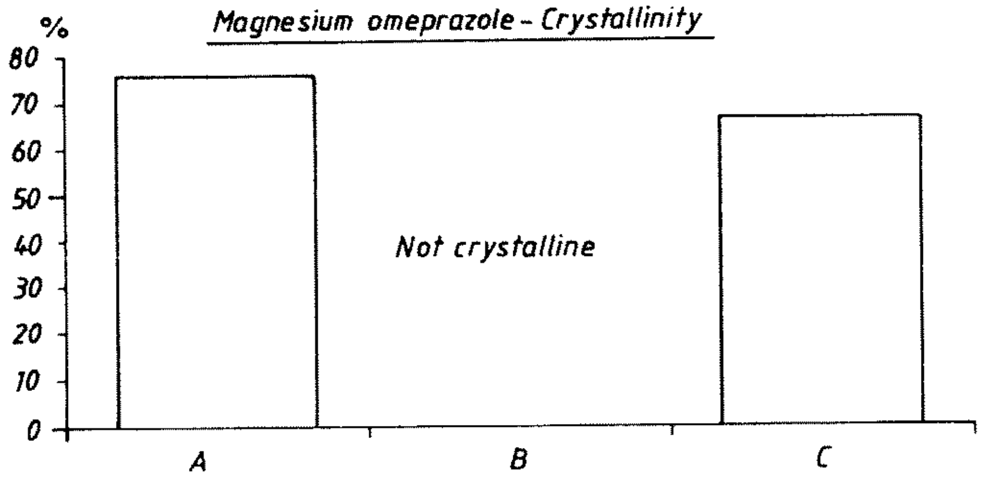

Magnesium omeprazole - Mean Mass Diameter
μm
100
90
80
70
60
50
40
30
20
10
0
>600
A
B
C

Fig. 2


Magnesium omeprazole - Crystallinity
%
80
70
60
50
40
30
20
10
0
Not crystalline
A
B
C

OMEPRAZOLE MAGNESIUM SALT FORM

This is a 371 of PCT/SE94/00680 filed Jul. 8, 1994, now WO 95/01977.

FIELD OF THE INVENTION

The present invention relates to a novel process for manufacturing the magnesium salt of omeprazole; the magnesium salt of omeprazole in a novel physical form, especially the magnesium salt as a product of the novel process; the use of the novel form of the magnesium salt of omeprazole in the manufacture of pharmaceutical formulations; and to the use of the novel form of the magnesium salt of omeprazole in medicine.

BACKGROUND OF THE INVENTION

The compound known under the generic name omeprazole is described i.a. in European patent specification 0005129.

Omeprazole is useful for inhibiting gastric acid secretion and has gastric mucosa protective activity in mammals and man. In a more general sense, omeprazole may be used for prevention and treatment of gastric acid related disorders and gastrointestinal inflammatory diseases in mammal and man, including e.g. gastritis, gastric ulcer and duodenal ulcer.

The term "omeprazole" as used in this specification designates the neutral form of the compound, that is the form without a salt forming cation present.

Certain salts of omeprazole are described in European patent specification 0124495. In said patent specification the requirements and importance regarding storage stability of pharmaceutical preparations are emphasized. Salts possessing superior properties with regard i.a. to storage stability are described in the said European patent specification. In EP 0124495; examples 5 and 6 disclose the synthesis of a magnesium salt of omeprazole.

The isolation and purification in full manufacturing scale of the described magnesium omeprazole salts presents one major problem in that magnesium omeprazole salt crystals are very fragile making processes utilising such crystals less attractive in full scale production. Performing the process without crystallization of the magnesium omeprazole gives a product which is less suitable as a pharmaceutical substance.

In order to use the magnesium salt of omeprazole, in this specification denoted magnesium omeprazole, in full manufacturing scale in preparing pharmaceutical formulations primarily for oral administration, such as tablets, it is necessary that said magnesium omeprazole possesses a combination of properties which makes such full scale manufacturing feasible. One object of the present invention is to provide a process for full scale production of magnesium omeprazole. A further object of the present invention is to provide a novel form of the magnesium salt of omeprazole which can be used in full scale manufacturing of pharmaceutical formulations, such as tablets.

The combination of physical properties of the novel magnesium omeprazole product of the present invention with respect to the degree of crystallinity, particle diameter, density, hygroscopicity, water content and content of other solvents are favorable and permit the manufacture of magnesium omeprazole in a form which possesses the desired properties.

The novel form of magnesium omeprazole can also be formulated into other forms for oral administration and other

types of administration such as rectal administration. Examples of formulations are tablets, pellets, granules, capsules, suspensions and suppositories.

The invention

We now provide a novel form of the magnesium salt of omeprazole exhibiting the desired combination of physical properties. This makes full scale production of magnesium omeprazole as well as full scale production of pharmaceutical formulations thereof feasible.

The novel process for the manufacture of magnesium omeprazole also circumvents the above described manufacturing problems and renders possible the recovery and work-up of the magnesium omeprazole substance in traditional chemical process equipment.

It has been found that the following property is significant to obtain such product:

a) Crystalline form, with a degree of crystallinity of not less than 70%, preferably higher than 75% as determined by X-ray powder diffraction

It is desirable that the product also exhibits the following properties;

b) Particle size measured as mean mass diameter (MMD) less than 30 μm, preferably less than 20 μm as determined by laser diffraction technique.

c) Density between 1.33 g/cm^3 and 1.35 g/cm^3 as determined by powder pycnometer.

d) Hygroscopicity not exceeding 2% increase of weight upon storage for one month up to 94% relative atmospheric humidity as determined gravimetrically.

e) A content of water of between 5% and 10% by weight as determined by titration according to Karl Fischer.

f) A content of methanol less than 0.1% preferably less than 0.05% by weight as determined by gas chromatography, in case methanol is used as solvent.

In a further aspect, the invention also relates to a process for manufacturing the novel form of magnesium omeprazole. This process is described in more detail below.

The invention relates to all of the aspects given under Field of the invention.

The process for producing the novel form of magnesium omeprazole is characterized by the following consecutive steps

a) treating omeprazole or a salt thereof with magnesium alcoholate in a solution

b) separating inorganic salts from the reaction mixture

c) crystallizing magnesium omeprazole

d) isolating the obtained crystalline magnesium omeprazole and, optionally,

e) purifying and drying the crystalline magnesium omeprazole using conventional methods.

The process for manufacturing the new product can be described in the following way.

A lower alcohol, such as methanol, ethanol, n-propanol or iso-propanol, preferably methanol, is treated in a solution of polar solvents with a weighed amount of magnesium at temperatures between 0° C. and reflux temperature. The temperature should preferably be between 10 and 30° C. After addition of the magnesium to the solution the temperature can, in a second step be raised further to between 0° C. and reflux temperature, preferably 20–50° C. After termination of the reaction the temperature is reduced to 0–40° C., preferably 10–25° C. Omeprazole or a salt of omeprazole is then added to the solution and after termination of the reaction the mixture is cooled to −10° C. to +20° C., preferably −5° C. to +5° C. The solvent is then evaporated to 40–60% of the initial volume, which makes the inorganic salts precipitate. The precipitate is separated from the reaction solution for example by centrifugation or filtration and the solution is heated to 5° C. to 30° C. whereafter the solution is seeded with magnesium omeprazole crystals. An amount of water, which is approximately equal to the volume of the solution, is added to start the crystallization. The solution is cooled to −10 to +20° C., preferably 0–10° C. to complete the crystallization. The crystals are then separated from the mother liquid for example by centrifugation or filtration and washed with polar solvents preferably an aqueous lower alcohol such as aqueous methanol. Finally, the produced crystals are dried preferably under reduced pressure and heating.

The process for manufacturing the new form of magnesium omeprazole differs from the earlier known processes in that the product is recovered after a controlled crystallization step in aqueous alcohol, preferably methanol by, first, separating the inorganic salts from the mother liquour. The crystallinity resulting from this step is, unexpectedly, higher and the product possesses a higher degree of purity and is more stable to decomposition from uptake of moisture. The drying step can be performed without caking. The new process is possible to perform in conventional chemical process equipment and gives a product with a higher yield than the processes hitherto known.

The following detailed Example 1 will serve to more fully illustrate the process for manufacturing magnesium omeprazole in full scale according to the present invention. In FIGS. **1** and **2** sample A is manufactured according to this example.

EXAMPLE 1

A reactor was filled with 2026 liters of methanol. The stirrer was started and the temperature was adjusted to 20° C. 3,90 kg of magnesium was added to the vessel and immediately thereafter 1,0 liter of CH_2Cl_2. The reactor was heated to 40° C. and kept at this temperature for 60 min. It was then cooled to 15° C. before the addition of 99,9 kg of omeprazole. The reactor was kept at this temperature for 60 min and then cooled to 0° C. The temperature was kept at this level for 30 minutes before 1000 l of methanol were evaporated under vacuum and the inorganic solid salt was separated from the liquid first by centrifugation and then by filtration. The liquid was heated to 10° C. and the liquid was seeded with magnesium omeprazole crystals whereafter the magnesium omeprazole salt was precipitated by addition of 900 l of water. The mixture was then cooled to 5° C. After the crystallization had been completed the magnesium omeprazole crystals were centrifuged off and then washed with a mixture of 50 l of methanol and 150 l of water. The produced magnesium omeprazole was dried under reduced pressure finally producing 92,5 kg of crystalline product corresponding to a yield of 81,4%.

The novel form of the magnesium salt of omeprazole according to Example 1 possesses the following properties:

a) Crystalline form, with a degree of crystallinity of 76%, as determined by X-ray powder diffraction.

b) Particle size measured as mean mass diameter (MMD) of 19 μm as determined by laser diffraction technique.

c) Density of 1.342 g/cm^3 as determined by powder pycnometer.

d) Hygroscopicity of 1.62% increase of weight upon storage for one month at 94% relative atmospheric humidity as determined gravimetrically.

e) Content of moisture water of 7.6 by weight as determined by titration according to Karl Fischer.

f) Content of methanol of 0.006% by weight as determined by gas chromatography.

A comparison between two different samples of the novel form of magnesium omeprazole of the present invention obtained from two laboratory scale experiments by prior art methods and magnesium omeprazole goes forth from diagrams 1 and 2. In these diagrams sample A represents the novel form of the present invention as manufactured in full scale process equipment. Sample B represents the product of preparation via synthesis by treatment of omeprazole with $Mg(OCH_3)_2$. Sample C represents the product of preparation via treatment of sodium omeprazole with $MgCl_2$.

FIG. **1** shows in diagram 1 that the particle size measured as mean mass diameter of the product of method A is 19 μm which is smaller than the corresponding particle size for the products of method B which is 25 μm and of method C which is greater than 600 μm.

FIG. **2** shows in diagram 2 that the degree of crystallinity of the particles of the product of method A is 76% which is higher than the corresponding figure for the product of sample B, which is 0% and also higher than the corresponding figure of sample C, which 67%.

What is claimed is:

1. An omeprazole magnesium salt having a degree of crystallinity which is higher than 70% as determined by x-ray powder diffraction.

2. The omeprazole magnesium salt according to claim **1** wherein the degree of crystallinity is higher than 75%.

3. The omeprazole magnesium salt according to claim **1** wherein the mean particle diameter as determined by laser diffraction technique is less than 30 μm, and preferably less than 20 μm.

4. The omeprazole magnesium salt according to claim **1** wherein the density is between 1.33 g/cm^3 and 1.35 g/cm^3 as determined by powder pycnometer.

5. The omeprazole magnesium salt according to claim **1** wherein the water content is between 5% and 10% by weight as determined by titration according to Karl Fischer.

6. The omeprazole magnesium salt according to claim **1** having a solvent content less than 0.1% by weight of solvent as determined by gas chromatography.

7. The omeprazole magnesium salt according to claim **1** having a solvent content less than 0.05% by weight of solvent as determined by gas chromatography.

8. The omeprazole magnesium salt of claim **6** or **7**, wherein the solvent is an aqueous alcohol.

9. The omeprazole magnesium salt of claim **6** or **7**, wherein the solvent is methanol.

10. The omeprazole magnesium salt according to claim **1** wherein the hygroscopicity is less than 2% increase of weight upon storage for one month at up to 94% relative atmospheric humidity as determined by gravimetry.

11. A process for the manufacture of magnesium omeprazole according to claim **1** comprising in consecutive steps

a) treating omeprazole or salt thereof with magnesium alcoholate in a solution,

b) separating inorganic salts from the reaction mixture,

c) crystallizing magnesium omeprazole by the addition of water, and

d) isolating the obtained crystalline magnesium omeprazole.

12. A process according to claim **11** wherein the magnesium alcoholate is magnesium methyl alcoholate.

13. A process according to claim **11** wherein the solvent is methanol.

14. A process according to claim **11** wherein the isolation of the magnesium omeprazole is performed by centrifugal separation of the crystals.

15. A process according to claim **11** wherein the isolation of the magnesium omeprazole is performed by crystallization followed by filtration of the crystals.

16. The process according to claim **11**, further comprising the steps of purifying and drying the crystalline magnesium omeprazole.

17. A process according to claim **16** wherein the purification of the magnesium omeprazole crystals is performed by washing the crystals with a solution of polar solvents.

18. A process according to claim **16** wherein the magnesium omeprazole crystals are dried under reduced pressure.

19. A process according to claim **16** wherein the drying of the magnesium omeprazole crystals is performed by evaporating the remaining solvent by heating.

20. In a process for the manufacture of a crystalline magnesium salt comprising, (a) treating omeprazole or a salt thereof with magnesium alcoholate in a solution, (b) crystallizing magnesium omeprazole and (c) isolating the obtained crystalline magnesium omeprazole, wherein the improved process comprises separating inorganic salts from the reaction mixture prior to the crystallization step by the addition of water.

21. A method for inhibiting gastric acid secretion in mammals and man comprising administering to a host in need thereof a therapeutically effective dose of magnesium omeprazole according to any of claims **1** to **4**, **6–8** and **10**.

22. A method for the treatment of gastric acid related diseases in mammals and man comprising administering to a host in need thereof a therapeutically effective dose of magnesium omeprazole according to any of claims **1** to **4**, **6–8** and **10**.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,900,424

DATED : May 4, 1999

INVENTOR(S) : Kallstrom et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 21, col. 6, line 9, delete "claims 1 to 4, 6-8" and insert therefor -- claims 1-7 --.

In claim 22, col. 6, lines 13-14, delete "claims 1 to 4, 6-8" and insert therefor -- claims 1-7 --.

Signed and Sealed this

Twenty-eighth Day of September, 1999

Attest:

Q. TODD DICKINSON

Attesting Officer

Acting Commissioner of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,900,424

DATED : May 4, 1999

INVENTOR(S) : Kallstrom et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page:

After "[56] References Cited," insert

-- U.S. PATENT DOCUMENTS

4,738,974	4/1988	514/338
5,690,960	11/1997	424/480
5,714,504	3/1998	514/338--

Signed and Sealed this

Fourth Day of January, 2000

Attest:

Attesting Officer

Acting Commissioner of Patents and Trademarks

EXHIBIT C

US006147103A

United States Patent [19]

Anousis et al.

[11] **Patent Number: 6,147,103**

[45] **Date of Patent: Nov. 14, 2000**

[54] **OMEPRAZOLE PROCESS AND COMPOSITIONS THEREOF**

[75] Inventors: **Nick Anousis**; **James W. McManus**; **Benjamin Newton Banks**, all of Albany, Ga.; **Lingwen Zhou**, North Brunswick, N.J.

[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[21] Appl. No.: **09/387,945**

[22] Filed: **Sep. 1, 1999**

Related U.S. Application Data

[62] Division of application No. 09/169,231, Oct. 9, 1998.
[60] Provisional application No. 60/096,037, Aug. 11, 1998.

[51] **Int. Cl.**[7] **A61K 31/415**
[52] **U.S. Cl.** **514/394**; 514/395
[58] **Field of Search** 514/394, 395

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,255,431	3/1981	Junggren et al.	424/263
5,386,032	1/1995	Brändström et al.	546/271
5,391,752	2/1995	Hoerrner et al.	546/271

FOREIGN PATENT DOCUMENTS

0 484 265 A1	6/1992	European Pat. Off. .
0 302 720 B1	11/1992	European Pat. Off. .
539793	1/1985	Spain .
540147	2/1985	Spain .
550070	12/1985	Spain .
2239453	3/1991	United Kingdom .
96/38175	12/1996	WIPO .
WO 98/40377	9/1998	WIPO .
WO 98/40378	9/1998	WIPO .
WO 98/09962	12/1998	WIPO .

Primary Examiner—Kevin E. Weddington
Attorney, Agent, or Firm—Philippe L. Durette; Melvin Winokur

[57] **ABSTRACT**

The present invention describes an improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole whereby the sulfide precursor pyrmetazole is reacted subsurfacely with exactly one molar equivalent of meta-chloroperoxybenzoic acid in methylene chloride or toluene solution; residual organic solvent is removed from the aqueous layer by vacuum distillation; crude product is obtained by reactive crystallization with an alkyl formate and seeding; and pure product is isolated by recrystallization in methanol-water containing aqueous NaOH by subsurface addition of aqueous acetic acid to pH 9.0, seeding, filtration, washing, and drying. Compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent are also described.

8 Claims, No Drawings

OMEPRAZOLE PROCESS AND COMPOSITIONS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional of Ser. No. 09/169,231, filed Oct. 9, 1998, which in turn is related to U.S. provisional application Ser. No. 60/096,037 filed Aug. 11, 1998, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention provides a novel improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole. Compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent are also disclosed.

BACKGROUND OF THE INVENTION

Omeprazole, the generic name for 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (denoted as Formula I below) is a well-described gastric proton-pump inhibitor and is on the market as LOSEC® or PRILOSEC® for the treatment of gastric and duodenal ulcers, gastritis, duodenitis, and reflux esophagitis (see Merck Index, 12th Ed., entry 6977, and references cited therein). Omeprazole is commercially prepared via a multi-step sequence, the last step of which is oxidation of the sulfide intermediate, 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]methylthio]-1H-benzimidazole (denoted as Formula II below), known generically as pyrmetazole, which is typically effected with a peroxy acid, such as meta-chloroperoxybenzoic acid (hereinafter referred to as MCPBA) (U.S. Pat. Nos. 4,255,431 and 5,386,032), magnesium monoperoxyphthalate (MMPP) (U.S. Pat. No. 5,391,752), or peroxyacetic acid (WO 98/09962), in a suitable non-alcoholic organic reaction solvent. The preferred oxidizing agent is usually MCPBA, and suitable non-alcoholic organic reaction solvents include aromatic hydrocarbon solvents, such as benzene and toluene, and chlorinated aliphatic hydrocarbon solvents, such as chloroform and methylene chloride, in admixture with an alcoholic solvent, such as methanol, ethanol, isopropanol, or 1-butanol. The preferred non-alcoholic organic reaction solvents are usually methylene chloride and toluene, and the preferred alcoholic solvent is ethanol.

Prior processes to omeprazole have numerous disadvantages that limit both the yield and the purity of the final product.

A significant drawback of such prior methods is incomplete oxidative conversion of pyrmetazole into omeprazole as well as non-chemoselective oxidation. Two aspects of chemoselectivity are important in the oxidation of pyrmetazole. First, pyrmetazole contains two tertiary amino groups which can compete with the sulfide group for the oxidizing agent. Although these amino groups are less reactive than the desired sulfide, they can nevertheless undergo quantitative oxidation with MCPBA below ambient temperature. Second, the product omeprazole (a sulfoxide) can also react with MCPBA to form a sulfone by-product. Non-chemoselectivity and over-oxidation, characteristic of the previous methods, arise from ineffective control over the amount of the oxidizing agent as well as the manner in which the oxidizing agent is charged into the reaction vessel. Prior methods do not use accurately determined amounts of the oxidizing agent and do not provide for careful control of its addition to the reaction mixture. Non-chemoselective, over-, and under-oxidation all contribute to high impurities and loss of yield of the final desired product.

Another disadvantage of prior procedures is the considerable loss of product in the purification and isolation steps due to solubility of omeprazole in the mother liquors and solvent washes.

A further drawback concerns diminished product quality resulting from occlusion of residual solvents and reaction by-products during the crystallization steps. It is desirable to eliminate residual levels of organic reaction solvent and recrystallization solvent impurities in the final crystalline product for toxicity/safety reasons.

It is therefore an object of the present invention to provide an improved process for the preparation, purification, and isolation of omeprazole that overcomes the yield and product purity limitations of prior methods.

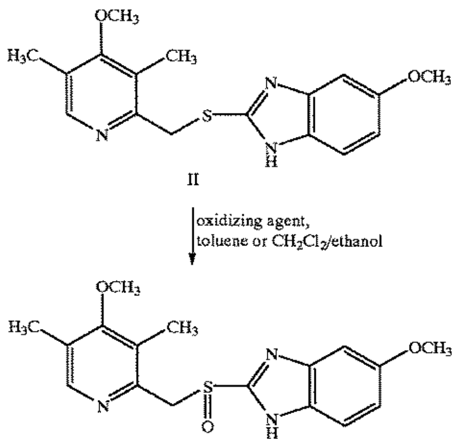
It is also an object of the invention to provide compositions of omeprazole having lower levels of residual non-alcoholic organic reaction solvent after the initial crude reactive crystallization step.

It is a further object of the present invention to provide final compositions of omeprazole that contain no residual non-alcoholic organic reaction solvent within the limits of chromatographic detection and less than 20 p.p.m. of residual crystallization solvent.

SUMMARY OF THE INVENTION

The present invention provides an improved process for the preparation, purification, and isolation of omeprazole of the Formula I.

The last chemical transformation in the preparation of omeprazole is the oxidative conversion of the sulfide intermediate pyrmetazole of the Formula II into its sulfoxide derivative omeprazole of the Formula I.



I

In one embodiment of the improved process, the oxidizing agent is meta-chloroperoxybenzoic acid (MCPBA), and the non-alcoholic organic reaction solvent is methylene chloride or toluene in admixture with an alcoholic solvent, such as methanol, ethanol, isopropanol, or 1-butanol, in particular, ethanol. In this embodiment, the completeness and chemoselectivity of the oxidation have been optimized by careful control of the amount of MCPBA charged to the reaction vessel. The use of one molar equivalent of MCPBA relative to the number of moles of pyrmetazole prevents non-chemoselective, over-, and under-oxidation resulting in fewer impurities and higher yields. In another embodiment of the present invention, the concentration of MCPBA in the charging solution is calculated using a novel analytical method based upon MCPBA oxidation of 3-methylisoquinoline to its N-oxide derivative and subsequent HPLC quantitation. Without this assay there exists no practical way to avoid either over-oxidation or incomplete conversion of pyrmetazole into omeprazole.

In a further embodiment of the present invention, control over localized over-oxidation is achieved by subsurface addition of MCPBA, providing for entry of the oxidizing solution into the reaction vessel at the tip of the agitator blades, with simultaneous control of the reaction temperature. Incorporation of these novel features into the process ensures complete conversion of pyrmetazole into omeprazole with no formation of sulfone by-products.

In another embodiment of the present invention, the isolation of the crude product has been improved by vacuum distillation of the crude aqueous phase after extraction of the reaction mixture prior to crystallization to remove most of the entrained methylene chloride or toluene from the oxidation step. The alcoholic solvent, in particular ethanol, concentration is re-adjusted in order to promote good crystal growth during the crude crystallization step. The crystallization step involves a two-stage neutralization with a C_{1-3} alkyl formate, preferably methyl formate, which is added subsurfacely through a diptube located near and directed perpendicular to the impeller tip. This mode of addition of the methyl formate ensures rapid dispersion of the neutralizing agent, which promotes crystal growth over spontaneous nucleation. In so doing, occlusion of mother liquors in the crystals is minimized. Lowering the concentration of ammonia, relative to that used in prior procedures, in the ammonia-water wash, necessary to remove color impurities in the crude product, provides for further improvement in the yield of omeprazole.

A further embodiment of the present invention concerns the final purification step. A methanol-water mixture is used for the crystallization step which is initiated by subsurface addition of aqueous acetic acid and subsequent seeding with omeprazole. The same methanol-water mixture is employed as a displacement wash to remove mother liquors and dissolved impurities while suppressing solubility losses. In this fashion, significant yield improvements are obtained with no adverse impact on product quality.

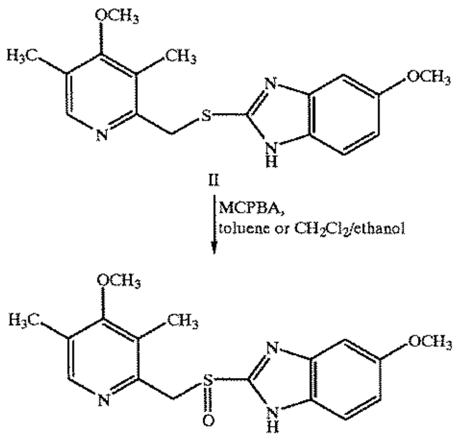
Crystalline omeprazole is thus obtained with significant improvement in yield and purity. The isolated material contains no chromatographically detectable levels of residual non-alcoholic organic reaction solvent and less than 20 p.p.m. of residual methanol as the crystallization solvent.

BRIEF DESCRIPTION OF THE DRAWINGS

Not Applicable

DETAILED DESCRIPTION OF THE INVENTION

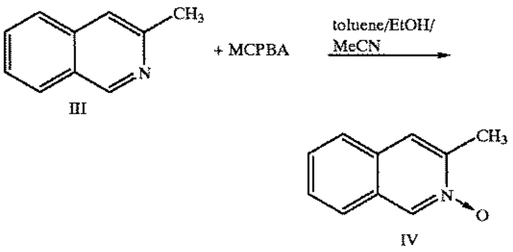
The instant invention relates to an improved process for the preparation, purification, and isolation of the proton-pump inhibitor omeprazole and to novel compositions thereof. Omeprazole, having formula I, is prepared by reacting a solution of pyrmetazole, having Formula II, cooled to about −5 to +5° C. and buffered to a pH of about 5 to 6,



I

with one molar equivalent of an oxidizing agent, relative to the number of moles of pyrmetazole, dissolved in a non-alcoholic organic reaction solvent in admixture with an alcoholic solvent. The alcoholic solvent is selected from methanol, ethanol, isopropanol, and 1-butanol.

In one embodiment of the instant improved process, the buffered solution comprises potassium bicarbonate, the oxidizing agent is meta-chloroperoxybenzoic acid, and the non-alcoholic organic reaction solvent is methylene chloride or toluene, either in admixture with ethanol. The reaction is carried out such that both completeness and chemoselectivity of the oxidation are optimized. To force the reaction to proceed in a near quantitative fashion, it is necessary that any excess of the oxidizing agent, MCPBA, be minimized. Hence, the solution containing the oxidizing agent is accurately assayed so that an exact amount of reagent will be charged to the reaction vessel. In prior methods, the amount of MCPBA added was based on the commercial supplier's assay number. Since MCPBA solid contains about 15–25% water for safety reasons, the solid is not homogeneous. Therefore, the manufacturer can provide only the average assay results of MCPBA. If MCPBA from different containers and different suppliers is used, an inaccurate charge of MCPBA will result. A novel analytical method has therefore been developed to quantify MCPBA in the charging solution in order to deliver an accurate amount of the oxidizing agent. According to the assay, an excess amount of 3-methylisoquinoline (III) is reacted with CPBA in toluene/ethanol solution to form 3-methylisoquinoline N-oxide (IV), according to the equation:



The reaction is fast and quantitative. The remaining tertiary amine in the reaction mixture is quantitated by reverse-phase high-performance liquid chromatography (RP-HPLC). The amount of the amine consumed during the reaction is used to calculate the concentration of the MCPBA solution.

It is also important that no excess oxidizing agent accumulate during addition of the reagent. This is best accomplished by subsurface addition of MCPBA, such that the solution enters the batch through a diptube located near and directed perpendicular to the agitator blades. This mode of addition provides for immediate dispersion of the oxidant, thus limiting localized over-oxidation.

Chemoselectivity and extent of oxidation are also enhanced by controlling the reaction temperature without crystallization of the oxidizing agent. The optimum temperature range is about 0–5° C. for the solution of the oxidizing agent and about −5 to +5° C. for the reaction mixture throughout the addition process. Higher temperatures of either the MCPBA solution or the reaction mixture will result in some sulfone formation. Likewise, much lower temperatures temporarily suppress the oxidation reaction, which results in a localized accumulation of the oxidizing a gent that can lead to over-oxidation products.

After addition of the solution containing the oxidizing gent, aqueous base, for example 50% NaOH or KOH, is added, the solution allowed to age for about 0.5–1.0 hours at 0–5° C., and the aqueous phase separated from the organic phase. To minimize residual levels of the non-alcoholic organic reaction solvent, in particular toluene or methylene chloride, in the crude product, which translates into higher levels of volatile non-alcoholic organic reaction solvent in the pure product, it is important to remove as much entrained toluene or methylene chloride as possible from the crude aqueous phase. The source of residual toluene or methylene chloride is an emulsion that forms when the crude batch is extracted from toluene or methylene chloride with aqueous base. Removal of residual solvent may be accomplished by vacuum distillation of the aqueous phase at a pressure of about 25–70 mm Hg and temperature of about 15–35° C. for about 1–4 hours. In further exemplification, the distillation is carried out at about 50 mm Hg and about 15° C. for 2 hours. The vacuum distillation procedure reduces the pre-crystallization levels of toluene or methylene chloride to less than 400 p.p.m. Other options to break up the emulsion and effect better phase separation are less effective; these include filtration of the crude aqueous phase through a bed of Celite™, increasing the settling time, and addition of a strong electrolyte.

Since the distillation process also results in removal of the alcohol, in particular ethanol, its concentration must be re-adjusted to approximately 15%, in order to facilitate crystal growth during the crude crystallization process. A lower level of the alcoholic solvent, in particular ethanol, produces finer crystals which are more likely to dissolve during subsequent washes thereby diminishing yields of the crude product.

At this point, the reactive crystallization of omeprazole is initiated and maintained under controlled conditions. Approximately 40% of a C_{1-3}-alkyl formate charge, preferably methyl formate, is added over the first 30 minutes to bring the batch from a pH of about 13.5 to near supersaturation at a pH of about 10.6 to 10.8. The methyl formate addition is accomplished through a diptube which is narrowed at one end to create a fine stream and which is located near and perpendicular to the impeller tip. This technique ensures rapid dispersion of the methyl formate so that occlusion of impurities is minimized. When a pH of about 10.6–10.8 is attained, the methyl formate addition is discontinued, and the batch is aged for ten to twenty minutes to allow the temperature to cool to approximately 20° C. prior to seeding. It is important to seed between pH 10.6 and 10.8. Below 10.6 spontaneous nucleation will occur with little crystal growth, if a sufficient seed bed is not present. Seeding is effected with pure, milled omeprazole (100% by HPLC), and the rest of the methyl formate is added subsurfacely over 6–8 hours to adjust the pH to about 9.0–9.3. This crystallization procedure improves both the yield and purity of the product. Without being held to a specific mechanism, it is believed that the purity enhancement is mainly due to preventing occlusion of mother liquors by promoting crystal growth over nucleation. Crude omeprazole at this stage contains less than 100 p.p.m. of residual toluene or methylene chloride, as determined by gas-liquid chromatographic analysis.

The crude crystallized product is then filtered, washed with 0.01–1.0%, preferably 0.1%, ammonia-water, and then methanol.

The crude wet omeprazole is then purified by dissolving it in 2:1–0.5–1 (v/v) methanol-water solution containing aqueous base, preferably 50% NaOH or KOH, at 20° C., cooling the basic solution to about 0–5° C., reducing the pH from >11.0 to approximately 10.5 by subsurface addition through a narrowed end diptube (configuration of apparatus same as in crude isolation step) of aqueous acetic acid, preferably 25% aqueous acetic acid, over a 30-minute period, while maintaining the temperature at 0–5° C. At this point the batch is seeded with pure omeprazole (100% by HPLC), and the subsurface addition of 25% aqueous acetic acid is continued over a 2–4 hour period until a pH of about 9.0 is attained. The batch is then aged for 0.5–1.0, preferably 0.5, hours. Following the aging period, the product is filtered, washed with the same methanol-water mixture to displace the mother liquors containing the impurities, and finally with cold methanol. Pure omeprazole is obtained after vacuum drying with a nitrogen purge at 30–50 mm Hg and 30–35° C.

The optimal methanol-water ratio in this final purification step is 1:1. Previous methods used a higher methanol to water ratio. Lowering the proportion of methanol in the solvent mixture used in the displacement wash minimizes solubility losses and provides the purification demands, thereby improving the yield of the final product without compromising product quality.

Crystalline omeprazole obtained using the improved process of the instant invention has an HPLC purity of 100% with no detectable levels of entrained residual toluene or methylene chloride from the crude step as measured by gas-liquid chromatography, the detection limit being 3 p.p.m. Prior methods have afforded omeprazole containing 30–100 p.p.m. of residual non-alcoholic organic reaction solvent, namely toluene or methylene chloride. The pure product contains less than 20 p.p.m. of residual methanol as the crystallization solvent.

For the preparation of pharmaceutical compositions in the form of dosage units for oral administration, omeprazole prepared according to the process of the present invention may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as an antifriction agent such as magnesium stearate, calcium stearate, and polyethyleneglycol waxes. The mixture is then pressed into tablets. If coated tablets are desired, the above-prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide, or with a lacquer dissolved in volatile organic solvent or mixture of solvents. To this coating various dyes may be added in order to distinguish among tablets with different amounts of active compound present.

Soft gelatin capsules may be prepared which contain a mixture of pure omeprazole prepared according to the process of the present invention and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin.

Pharmaceutical tablets for oral use are prepared in the following manner. The solid substances are ground or sieved to a certain particle size, and the binding agent is homogenized and suspended in a suitable solvent. The solid omeprazole prepared according to the process of the present invention and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension having the consistency of wet snow. The moistening causes the particles to aggregate slightly, and the resulting mass is pressed through a stainless steel sieve having a mesh size of about 1 millimeter. The layers of the mixture are dried in carefully controlled drying cabinets for approximately ten hours to obtain the desired particle size and consistency. The granules of the dried mixture are sieved to remove any powder. To this mixture, disintegrating, antifriction, and antiadhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The pressure applied affects the size of the tablet, its strength and ability to dissolve in water. The compression pressure used should be in the range of 0.5 to 5 tons. The tablets, especially those which are rough or bitter, may be coated with a layer of sugar or some other palatable substance. They are then packaged by machines having electronic counting devices.

The following examples illustrate the process of the present invention and are not intended to limit the scope of the invention set forth in the claims appended thereto.

EXAMPLE 1

HPLC Assay of MCPBA Charging Solution

Step A. HPLC Operating Parameters

High-performance liquid chromatography was performed using a Waters μBondapak C-18 column (4.6×300 mm, 10 μm particle size) with the following additional parameters:

Mobile phase: A=acetonitrile; B=0.1% H_3PO_4

Mode: isocratic 25%A/75%B at a flow rate of 1.0 mL/min

Injection size: 10 μL

Detector wavelength: 254 nm

Run time: 32 min.

Method of quantitation: Area by electronic integration

Approximate retention times: 3-methylisoquinoline: 3.5 mins.

3-methylisoquinoline N-oxide: 5.7 mins.

MCPBA: 11.4 mins.

Toluene: 25.1 mins.

Step B.	Reagents	
	Acetonitrile (MeCN):	HPLC Grade
	Water:	HPLC Grade
	Phosphoric Acid:	HPLC Grade
	3-Methylisoquinoline:	98%
	Sample Diluent:	50/50 (MeCN/0.1% H_3PO_4)

Step C. Preparation of 3-Methylisoguinoline Standard

20±5 mg of 3-methylisoquinoline (98%) was transferred into a 10 mL volumetric flask and dissolved in 1.0 mL of MeCN. 1.0 mL of MCPBA after warming to room temperature was carefully pipetted into the flask, and the sides of the flask were washed with 1.0 mL of MeCN. The flask was then wrapped with parafilm and sonicated for 5 minutes. After cooling, the sides of the flask were washed with 1.0 mL of MeCN and the flask sonicated for an additional minute. The mixture was carefully diluted to the mark with acetonitrile. 1.0 mL of this solution was transferred by pipet to a 25-mL volumetric flask and diluted to the mark with the sample diluent from Step B.

Step D. Procedures

The HPLC system was equilibrated for at least 10 minutes at the mobile phase condition given in Step A. The standard preparation from Step C was injected twice, and the average area response for the 3-methylisoquinoline peaks should agree within ±1% of their average. The sample preparation was injected once.

Step E. Calculations

The concentration (mg/mL) of the MCPBA solution was calculated using the following equation:

$$\text{mg/mL of MCPBA solution} = (w-(A/As)\times Cs\times 250)\times\frac{172.57}{143.19}$$

where:

A=area response of the 3-methylisoquinoline for the Sample Solution

B=weight (mg) of the 3-methylisoquinoline in the Sample Preparation

As=average area response of the 3-methylisoquinoline for the Standard Solution

Cs=concentration of the 3-methylisoquinoline Standard Preparation

172.57=formula weight for 3-methylisoquinoline

143.19=formula weight for MCPBA

As an illustration of the assay, an MCPBA sample from Spectrum (Lot# LF0102, 72.7% MCPBA) was assayed, and a value of 72.8% (wt. %) for MCPBA was obtained.

EXAMPLE 2

Preparation of Omeprazole with Methylene Chloride as Solvent

A solution of potassium bicarbonate (14.0 g, 0.140 mol, 1.2 equivalents) in deionized water (115 mL) was added to a solution of pyrmetazole (0.114 mol) in methylene chloride (170 mL) in a one-liter, three-necked round-bottom flask, and the mixture was cooled to 0° C. A solution of meta-chloroperoxybenzoic acid (MCPBA) (28 g, 0.114 mol, 1.0 equivalent) in methylene chloride (51 mL) and ethanol (13.3 mL) was prepared and assayed by the 3-methylisoquinoline/HPLC procedure described in Example 1 to ensure that exactly one molar equivalent of MCPBA is used. The solution is then cooled between 0–5° C. and added, subsurfacely directed at the tip of the impeller, to the rapidly agitated solution of pyrmetazole over a 2-hour period. The oxidation conversion was 99.8% with no over-oxidation to sulfone or N-oxides, as determined by HPLC analysis. Cold deionized water (115 mL, 5° C.) and 50% NaOH (15 mL) were then added to the reaction mixture. The solution was allowed to stand at 0–5° C. for thirty minutes and the phases separated. The methylene chloride layer was discarded and the aqueous layer concentrated under vacuum (50 mm Hg) for 2 hours at 15° C. to remove the bulk of the residual methylene chloride. The ethanol level was then re-adjusted to 15% v/v. At this point the residual methylene chloride level was less than 200 p.p.m., as determined by gas-liquid chromatographic analysis.

The crude product was then isolated by reactive crystallization by subsurface addition of methyl formate. Approximately 40% of the methyl formate charge (approximately 6 mL) was added during the first thirty minutes to adjust the pH from about 13.5 to 10.8. The mixture was allowed to stand for about twenty minutes to allow the internal temperature to cool back down to approximately 20° C. The mixture was seeded with pure omeprazole (0.5 g), and the remainder of the methyl formate (approximately 9 mL) was added subsurfacely over a 7-hour period to a pH of 9.0. The crude product was filtered, washed with 0.1% ammonia-water (50 mL) followed by methanol (40 mL).

The crude product was dissolved in 1:1 methanol-water (270 mL) and 50% NaOH (4 mL) in a 500-mL, three-necked, round-bottomed flask at 20° C. The solution was then cooled to 0–5° C. and the pH adjusted from >11.0 to approximately 10.5 by subsurface addition of 25% acetic acid over a 30-minute period, maintaining the temperature at 5° C. The batch was seeded with pure omeprazole (0.5 g), and the subsurface addition of 25% acetic acid was continued over a 4-hour period until pH 9.0 was achieved. After thirty minutes, the resulting solid was filtered, washed with 1:1 methanol-water (30 mL), and finally with cold (5° C.) methanol (30 mL). Pure omeprazole (100% as determined by HPLC analysis) was obtained after vacuum drying (50 mm Hg, 30–35° C.). The overall yield was 92.7%. The residual methanol level was 10 ppm, as determined by gas-liquid chromatography, with no detectable levels of methylene chloride (detection limit of 3 p.p.m.).

EXAMPLE 3

Preparation of Omeprazole with Toluene as Solvent

A solution of potassium bicarbonate (14.0 g, 0.140 mol, 1.2 equivalents) in deionized water (115 mL) was added to a solution of pyrmetazole (0.114 mol) in toluene (310 mL) in a one-liter, three-necked round-bottom flask, and the mixture was cooled to 0° C. Following the bicarbonate addition, a solution of meta-chloroperoxybenzoic acid (0.114 mol, 1 equivalent) in toluene (53 mL) and ethanol (20 mL) was assayed and charged to the pyrmetazole solution as in Example 2. The oxidation conversion was 99.8% with no over-oxidation to sulfone or N-oxides. Cold deionized water (145 mL, 5° C.) and 50% NaOH (12 mL) were then added to the reaction mixture. The solution was allowed to stand at 0–5° C. for thirty minutes and the phases separated. The toluene layer was discarded and the aqueous layer concentrated under vacuum (50 mm Hg) for 2 hours at 15° C. to remove the bulk of the residual toluene. The ethanol level was then adjusted to 15% v/v. At this point the residual toluene level was less than 400 p.p.m., as determined by gas-liquid chromatographic analysis.

The crude product was then isolated by reactive crystallization by subsurface addition of methyl formate as in Example 2. It was filtered, washed with 0.1% ammonia-water (50 mL) followed by methanol (40 mL). The wet crude product was then processed to pure omeprazole as in Example 2. The overall yield was 93.8% with an HPLC purity of 100%. The residual methanol level was 10 ppm, as determined by gas-liquid chromatography, with no detectable levels of toluene (detection limit 3 p.p.m).

EXAMPLE 4

A pharmaceutical composition containing omeprazole prepared according to the process of the present invention as the active ingredient is illustrated in the following formulation.

Capsules containing 30 mg of omeprazole of the present invention were prepared from the following ingredients:

Compound of Example 2 or 3	300 grams
Lactose	700 grams
Microcrystalline cellulose	40 grams
Hydroxypropyl cellulose, low substituted	62 grams
Disodium hydrogenphosphate	2 grams
Purified water	q.s.

The omeprazole of Example 2 or 3 was mixed with the dry ingredients and granulated with a solution of disodium hydrogenphosphate. The wet mass was forced through an extruder and sphreronized and dried in a fluidized bed dryer.

500 Grams of the pellets were coated with a solution of hydroxypropyl methylcellulose (30 grams) in water (750 mL) using a fluidized bed coater. After drying, the pellets were coated with a second coating as follows:

Coating solution:	
Hydroxypropyl methylcellulose phthalate	70 grams
Cetyl alcohol	4 grams
Acetone	200 grams
Ethanol	600 grams

The final coated pellets were filled into capsules.

What is claimed is:

1. A composition comprising 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) having less than three parts per million of residual aromatic hydrocarbon solvent and less than 20 p.p.m. of residual methanol relative to omeprazole.

2. A composition comprising 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) having less than three parts per million of residual chlorinated aliphatic hydrocarbon solvent and less than 20 p.p.m. of residual methanol relative to omeprazole.

3. The composition according to claim **1** wherein the aromatic hydrocarbon solvent is toluene.

4. The composition according to claim **2** wherein the chlorinated aliphatic hydrocarbon solvent is methylene chloride.

5. A pharmaceutical composition comprising 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) having less than three parts per million of residual aromatic hydrocarbon solvent and less than 20 p.p.m. of residual methanol relative to omeprazole, and a pharmaceutically acceptable excipient.

6. A pharmaceutical composition comprising 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole omeprazole) having less than three parts per million of residual chlorinated aliphatic hydrocarbon solvent and less than 20 p.p.m. of residual methanol relative to omeprazole, and a pharmaceutically acceptable excipient.

7. The pharmaceutical composition according to claim **5** wherein the aromatic hydrocarbon solvent is toluene.

8. The pharmaceutical composition according to claim **6** wherein the chlorinated aliphatic hydrocarbon solvent is methylene chloride.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,147,103
DATED : November 14, 2000
INVENTOR(S) : Nick Anousis, James W. Mc Manus, Benjamin Newton Banks, Lingwen Zhou

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claims,

Claim 1,
Lines 4-5, cancel "less than 20" and substitute therefor "10-20".

Claims 2, 5 and 6,
Line 5, in each, cancel "less than 20" and substitute therefor "10-20".

Signed and Sealed this

Sixth Day of November, 2001

Attest:

Nicholas P. Godici

NICHOLAS P. GODICI

Attesting Officer *Acting Director of the United States Patent and Trademark Office*

E X H I B I T D

US006166213A

United States Patent [19]

Anousis et al.

[11] **Patent Number: 6,166,213**

[45] **Date of Patent: Dec. 26, 2000**

[54] **OMEPRAZOLE PROCESS AND COMPOSITIONS THEREOF**

[75] Inventors: **Nick Anousis**; **James W. McManus**; **Benjamin Newton Banks**, all of Albany, Ga.; **Lingwen Zhou**, North Brunswick; **Hui Liu**, Greenbrook, both of N.J.

[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[21] Appl. No.: **09/169,231**

[22] Filed: **Oct. 9, 1998**

Related U.S. Application Data

[60] Provisional application No. 60/096,037, Aug. 11, 1998.

[51] **Int. Cl.**[7] **C07D 401/12**

[52] **U.S. Cl.** **546/273.7**

[58] **Field of Search** 546/273.7

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,635,520 6/1997 Uda et al. 514/338

FOREIGN PATENT DOCUMENTS

539.793 1/1985 Spain .

540.147 5/1985 Spain .

550.070 12/1985 Spain .

WO 98/40377 9/1998 WIPO .

WO 98/40378 9/1998 WIPO .

Primary Examiner—Patricia L. Morris

Attorney, Agent, or Firm—Philippe L. Durette; Melvin Winokur

[57] **ABSTRACT**

The present invention describes an improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole whereby the sulfide precursor pyrmetazole is reacted subsurfacely with exactly one molar equivalent of meta-chloroperoxybenzoic acid in methylene chloride or toluene solution; residual organic solvent is removed from the aqueous layer by vacuum distillation; crude product is obtained by reactive crystallization with an alkyl formate and seeding; and pure product is isolated by recrystallization in methanol-water containing aqueous NaOH by subsurface addition of aqueous acetic acid to pH 9.0, seeding, filtration, washing, and drying. Compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent are also described.

29 Claims, No Drawings

OMEPRAZOLE PROCESS AND COMPOSITIONS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

The present invention is related to U.S. provisional application Ser. No. 60/096,037 filed Aug. 11, 1998, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention provides a novel improved process for the preparation, isolation, and purification of the antiulcer agent omeprazole. Compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent are also disclosed.

BACKGROUND OF THE INVENTION

Omeprazole, the generic name for 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (denoted as Formula I below) is a well-described gastric proton-pump inhibitor and is on the market as LOSEC® or PRILOSEC® for the treatment of gastric and duodenal ulcers, gastritis, duodenitis, and reflux esophagitis (see Merck Index, 12th Ed., entry 6977, and references cited therein). Omeprazole is commercially prepared via a multi-step sequence, the last step of which is oxidation of the sulfide intermediate, 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]methylthio]-1H-benzimidazole (denoted as Formula II below), known generically as pyrmetazole, which is typically effected with a peroxy acid, such as meta-chloroperoxybenzoic acid (hereinafter referred to as MCPBA) (U.S. Pat. Nos. 4,255,431 and 5,386,032), magnesium monoperoxyphthalate MMPP) (U.S. Pat. No. 5,391,752), or peroxyacetic acid (WO 98/09962), in suitable non-alcoholic organic reaction solvent. The preferred xidizing agent is usually MCPBA, and suitable non-alcoholic organic reaction solvents include aromatic hydrocarbon solvents, such as benzene and toluene, and chlorinated aliphatic hydrocarbon solvents, such as chloroform and methylene chloride, in admixture with an alcoholic solvent, such as methanol, ethanol, isopropanol, or 1-butanol. The preferred non-alcoholic organic reaction solvents are usually methylene chloride and toluene, and the preferred alcoholic solvent is ethanol.

Prior processes to omeprazole have numerous disadvantages that limit both the yield and the purity of the final product.

A significant drawback of such prior methods is incomplete oxidative conversion of pyrmetazole into omeprazole as well as non-chemoselective oxidation. Two aspects of chemoselectivity are important in the oxidation of pyrmetazole. First, pyrmetazole contains two tertiary amino groups which can compete with the sulfide group for the oxidizing agent. Although these amino groups are less reactive than the desired sulfide, they can nevertheless undergo quantitative oxidation with MCPBA below ambient temperature. Second, the product omeprazole (a sulfoxide) can also react with MCPBA to form a sulfone by-product. Non-chemoselectivity and over-oxidation, characteristic of the previous methods, arise from ineffective control over the amount of the oxidizing agent as well as the manner in which the oxidizing agent is charged into the reaction vessel. Prior methods do not use accurately determined amounts of the oxidizing agent and do not provide for careful control of its addition to the reaction mixture. Non-chemoselective, over-, and under-oxidation all contribute to high impurities and loss of yield of the final desired product.

Another disadvantage of prior procedures is the considerable loss of product in the purification and isolation steps due to solubility of omeprazole in the mother liquors and solvent washes.

A further drawback concerns diminished product quality resulting from occlusion of residual solvents and reaction by-products during the crystallization steps. It is desirable to eliminate residual levels of organic reaction solvent and recrystallization solvent impurities in the final crystalline product for toxicity/safety reasons.

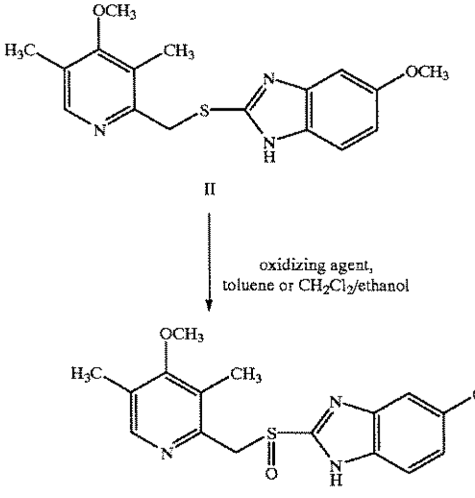
It is therefore an object of the present invention to provide an improved process for the preparation, purification, and isolation of omeprazole that overcomes the yield and product purity limitations of prior methods.

It is also an object of the invention to provide compositions of omeprazole having lower levels of residual non-alcoholic organic reaction solvent after the initial crude reactive crystallization step.

It is a further object of the present invention to provide final compositions of omeprazole that contain no residual non-alcoholic organic reaction solvent within the limits of chromatographic detection and less than 20 p.p.m. of residual crystallization solvent.

SUMMARY OF THE INVENTION

The present invention provides an improved process for the preparation, purification, and isolation of omeprazole of the Formula I. The last chemical transformation in the preparation of omeprazole is the oxidative conversion of the sulfide intermediate pyrmetazole of the Formula II into its sulfoxide derivative omeprazole of the Formula I.



In one embodiment of the improved process, the oxidizing agent is meta-chloroperoxybenzoic acid (MCPBA), and the non-alcoholic organic reaction solvent is methylene chloride or toluene in admixture with an alcoholic solvent, such as methanol, ethanol, isopropanol, or 1-butanol, in particular, ethanol. In this embodiment, the completeness and chemoselectivity of the oxidation have been optimized by careful control of the amount of MCPBA charged to the reaction vessel. The use of one molar equivalent of MCPBA relative to the number of moles of pyrmetazole prevents non-chemoselective, over-, and under-oxidation resulting in fewer impurities and higher yields. In another embodiment of the present invention, the concentration of MCPBA in the charging solution is calculated using a novel analytical method based upon MCPBA oxidation of 3-methylisoquinoline to its N-oxide derivative and subsequent HPLC quantitation. Without this assay there exists no practical way to avoid either over-oxidation or incomplete conversion of pyrmetazole into omeprazole.

In a further embodiment of the present invention, control over localized over-oxidation is achieved by subsurface addition of MCPBA, providing for entry of the oxidizing solution into the reaction vessel at the tip of the agitator blades, with simultaneous control of the reaction temperature. Incorporation of these novel features into the process ensures complete conversion of pyrmetazole into omeprazole with no formation of sulfone by-products.

In another embodiment of the present invention, the isolation of the crude product has been improved by vacuum distillation of the crude aqueous phase after extraction of the reaction mixture prior to crystallization to remove most of the entrained methylene chloride or toluene from the oxidation step. The alcoholic solvent, in particular ethanol, concentration is re-adjusted in order to promote good crystal growth during the crude crystallization step. The crystallization step involves a two-stage neutralization with a C_{1-3} alkyl formate, preferably methyl formate, which is added subsurfacely through a diptube located near and directed perpendicular to the impeller tip. This mode of addition of the methyl formate ensures rapid dispersion of the neutralizing agent, which promotes crystal growth over spontaneous nucleation. In so doing, occlusion of mother liquors in the crystals is minimized. Lowering the concentration of ammonia, relative to that used in prior procedures, in the ammonia-water wash, necessary to remove color impurities in the crude product, provides for further improvement in the yield of omeprazole.

A further embodiment of the present invention concerns the final purification step. A methanol-water mixture is used for the crystallization step which is initiated by subsurface addition of aqueous acetic acid and subsequent seeding with omeprazole. The same methanol-water mixture is employed as a displacement wash to remove mother liquors and dissolved impurities while suppressing solubility losses. In this fashion, significant yield improvements are obtained with no adverse impact on product quality.

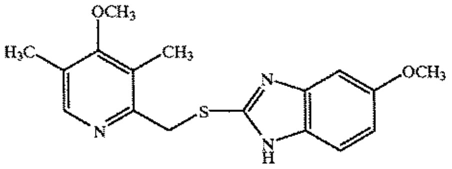
Crystalline omeprazole is thus obtained with significant improvement in yield and purity. The isolated material contains no chromatographically detectable levels of residual non-alcoholic organic reaction solvent and less than 20 p.p.m. of residual methanol as the crystallization solvent.

BRIEF DESCRIPTION OF THE DRAWINGS

Not Applicable

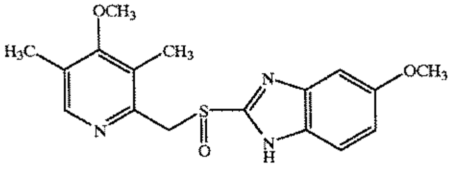
DETAILED DESCRIPTION OF THE INVENTION

The instant invention relates to an improved process for the preparation, purification, and isolation of the proton-pump inhibitor omeprazole and to novel compositions thereof. Omeprazole, having formula I, is prepared by reacting a solution of pyrmetazole, having Formula II, cooled to about −5 to +5° C. and buffered to a pH of about 5 to 6,



II

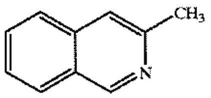
MCPBA, toluene or CH_2Cl_2/ethanol



I

with one molar equivalent of an oxidizing agent, relative to the number of moles of pyrmetazole, dissolved in a non-alcoholic organic reaction solvent in admixture with an alcoholic solvent. The alcoholic solvent is selected from methanol, ethanol, isopropanol, and 1-butanol.

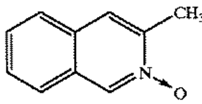
In one embodiment of the instant improved process, the buffered solution comprises potassium bicarbonate, the oxidizing agent is meta-chloroperoxybenzoic acid, and the non-alcoholic organic reaction solvent is methylene chloride or toluene, either in admixture with ethanol. The reaction is carried out such that both completeness and chemoselectivity of the oxidation are optimized. To force the reaction to proceed in a near quantitative fashion, it is necessary that any excess of the oxidizing agent, MCPBA, be minimized. Hence, the solution containing the oxidizing agent is accurately assayed so that an exact amount of reagent will be charged to the reaction vessel. In prior methods, the amount of MCPBA added was based on the commercial supplier's assay number. Since MCPBA solid contains about 15–25% water for safety reasons, the solid is not homogeneous. Therefore, the manufacturer can provide only the average assay results of MCPBA. If MCPBA from different containers and different suppliers is used, an inaccurate charge of MCPBA will result. A novel analytical method has therefore been developed to quantify MCPBA in the charging solution in order to deliver an accurate amount of the oxidizing agent. According to the assay, an excess amount of 3-methylisoquinoline (III) is reacted with MCPBA in toluene/ethanol solution to form 3-methylisoquinoline N-oxide (IV), according to the equation:



+ MCPBA $\xrightarrow{\text{toluene/EtOH/MeCN}}$

III

-continued



IV

The reaction is fast and quantitative. The remaining tertiary amine in the reaction mixture is quantitated by reverse-phase high-performance liquid chromatography (RP-HPLC). The amount of the amine consumed during the reaction is used to calculate the concentration of the MCPBA solution.

It is also important that no excess oxidizing agent accumulate during addition of the reagent. This is best accomplished by subsurface addition of MCPBA, such that the solution enters the batch through a diptube located near and directed perpendicular to the agitator blades. This mode of addition provides for immediate dispersion of the oxidant, thus limiting localized over-oxidation.

Chemoselectivity and extent of oxidation are also enhanced by controlling the reaction temperature without crystallization of the oxidizing agent. The optimum temperature range is about 0–5° C. for the solution of the oxidizing agent and about −5 to +5° C. for the reaction mixture throughout the addition process. Higher temperatures of either the MCPBA solution or the reaction mixture will result in some sulfone formation. Likewise, much lower temperatures temporarily suppress the oxidation reaction, which results in a localized accumulation of the oxidizing agent that can lead to over-oxidation products.

After addition of the solution containing the oxidizing agent, aqueous base, for example 50% NaOH or KOH, is added, the solution allowed to age for about 0.5–1.0 hours at 0–5° C., and the aqueous phase separated from the organic phase. To minimize residual levels of the non-alcoholic organic reaction solvent, in particular toluene or methylene chloride, in the crude product, which translates into higher levels of volatile non-alcoholic organic reaction solvent in the pure product, it is important to remove as much entrained toluene or methylene chloride as possible from the crude aqueous phase. The source of residual toluene or methylene chloride is an emulsion that forms when the crude batch is extracted from toluene or methylene chloride with aqueous base. Removal of residual solvent may be accomplished by vacuum distillation of the aqueous phase at a pressure of about 25–70 mm Hg and temperature of about 15–35° C. for about 1–4 hours. In further exemplification, the distillation is carried out at about 50 mm Hg and about 15° C. for 2 hours. The vacuum distillation procedure reduces the pre-crystallization levels of toluene or methylene chloride to less than 400 p.p.m. Other options to break up the emulsion and effect better phase separation are less effective; these include filtration of the crude aqueous phase through a bed of Celite™, increasing the settling time, and addition of a strong electrolyte.

Since the distillation process also results in removal of the alcohol, in particular ethanol, its concentration must be re-adjusted to approximately 15%, in order to facilitate crystal growth during the crude crystallization process. A lower level of the alcoholic solvent, in particular ethanol, produces finer crystals which are more likely to dissolve during subsequent washes thereby diminishing yields of the crude product.

At this point, the reactive crystallization of omeprazole is initiated and maintained under controlled conditions. Approximately 40% of a C_{1-3}-alkyl formate charge, preferably methyl formate, is added over the first 30 minutes to bring the batch from a pH of about 13.5 to near supersaturation at a pH of about 10.6 to 10.8. The methyl formate addition is accomplished through a diptube which is narrowed at one end to create a fine stream and which is located near and perpendicular to the impeller tip. This technique ensures rapid dispersion of the methyl formate so that occlusion of impurities is minimized. When a pH of about 10.6–10.8 is attained, the methyl formate addition is discontinued, and the batch is aged for ten to twenty minutes to allow the temperature to cool to approximately 20° C. prior to seeding. It is important to seed between pH 10.6 and 10.8. Below 10.6 spontaneous nucleation will occur with little crystal growth, if a sufficient seed bed is not present. Seeding is effected with pure, milled omeprazole (100% by HPLC), and the rest of the methyl formate is added subsurfacely over 6–8 hours to adjust the pH to about 9.0–9.3. This crystallization procedure improves both the yield and purity of the product. Without being held to a specific mechanism, it is believed that the purity enhancement is mainly due to preventing occlusion of mother liquors by promoting crystal growth over nucleation. Crude omeprazole at this stage contains less than 100 p.p.m. of residual toluene or methylene chloride, as determined by gas-liquid chromatographic analysis.

The crude crystallized product is then filtered, washed with 0.01–1.0%, preferably 0.1%, aammonia-water, and then methanol.

The crude wet omeprazole is then purified by dissolving it in 2:1–0.5–1 (v/v) methanol-water solution containing aqueous base, preferably 50% NaOH or KOH, at 20° C., cooling the basic solution to about 0–5° C., reducing the pH from >11.0 to approximately 10.5 by subsurface addition through a narrowed end diptube (configuration of apparatus same as in crude isolation step) of aqueous acetic acid, preferably 25% aqueous acetic acid, over a 30-minute period, while maintaining the temperature at 0–5° C. At this point the batch is seeded with pure omeprazole (100% by HPLC), and the subsurface addition of 25% aqueous acetic acid is continued over a 2–4 hour period until a pH of about 9.0 is attained. The batch is then aged for 0.5–1.0, preferably 0.5, hours. Following the aging period, the product is filtered, washed with the same methanol-water mixture to displace the mother liquors containing the impurities, and finally with cold methanol. Pure omeprazole is obtained after vacuum drying with a nitrogen purge at 30–50 mm Hg and 30–35° C.

The optimal methanol-water ratio in this final purification step is 1:1. Previous methods used a higher methanol to water ratio. Lowering the proportion of methanol in the solvent mixture used in the displacement wash minimizes solubility losses and provides the purification demands, thereby improving the yield of the final product without compromising product quality.

Crystalline omeprazole obtained using the improved process of the instant invention has an HPLC purity of 100% with no detectable levels of entrained residual toluene or methylene chloride from the crude step as measured by gas-liquid chromatography, the detection limit being 3 p.p.m. Prior methods have afforded omeprazole containing 30–100 p.p.m. of residual non-alcoholic organic reaction solvent, namely toluene or methylene chloride. The pure product contains less than 20 p.p.m. of residual methanol as the crystallization solvent.

For the preparation of pharmaceutical compositions in the form of dosage units for oral administration, omeprazole prepared according to the process of the present invention may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as an antifriction agent such as magnesium stearate, calcium stearate, and polyethyleneglycol waxes. The mixture is then pressed into tablets. If coated tablets are desired, the above-prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide, or with a lacquer dissolved in volatile organic solvent or mixture of solvents. To this coating various dyes may be added in order to distinguish among tablets with different amounts of active compound present.

Soft gelatin capsules may be prepared which contain a mixture of pure omeprazole prepared according to the process of the present invention and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin.

Pharmaceutical tablets for oral use are prepared in the following manner. The solid substances are ground or sieved to a certain particle size, and the binding agent is homogenized and suspended in a suitable solvent. The solid omeprazole prepared according to the process of the present invention and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension having the consistency of wet snow. The moistening causes the particles to aggregate slightly, and the resulting mass is pressed through a stainless steel sieve having a mesh size of about 1 millimeter. The layers of the mixture are dried in carefully controlled drying cabinets for approximately ten hours to obtain the desired particle size and consistency. The granules of the dried mixture are sieved to remove any powder. To this mixture, disintegrating, antifriction, and antiadhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The pressure applied affects the size of the tablet, its strength and ability to dissolve in water. The compression pressure used should be in the range of 0.5 to 5 tons. The tablets, especially those which are rough or bitter, may be coated with a layer of sugar or some other palatable substance. They are then packaged by machines having electronic counting devices.

The following examples illustrate the process of the present invention and are not intended to limit the scope of the invention set forth in the claims appended thereto.

EXAMPLE 1

HPLC Assay of MCPBA Charging Solution

Step A. HPLC Operating Parameters

High-performance liquid chromatography was performed using a Waters μBondapak C-18 column (4.6×300 mm, 10 μm particle size) with the following additional parameters:

Mobile phase: A=acetonitrile; B=0.1% H_3PO_4

Mode: isocratic 25%A/75%B at a flow rate of 1.0 mL/min

Injection size: 10 μL

Detector wavelength: 254 nm

Run time: 32 min.

Method of quantitation: Area by electronic integration

Approximate retention times:

3-methylisoquinoline: 3.5 mins.

3-methylisoquinoline N-oxide: 5.7 mins.

MCPBA: 11.4 mins.

Toluene: 25.1 mins.

Step B. Reagents

Acetonitrile (MeCN): HPLC Grade

Water: HPLC Grade

Phosphoric Acid: HPLC Grade

3-Methylisoquinoline: 98%

Sample Diluent: 50/50 (MeCN/0.1% H_3PO_4)

Step C. Preparation of 3-Methylisoquinoline Standard

20±5 mg of 3-methylisoquinoline (98%) was transferred into a 10 mL volumetric flask and dissolved in 1.0 mL of MeCN. 1.0 mL of MCPBA after warming to room temperature was carefully pipetted into the flask, and the sides of the flask were washed with 1.0 mL of MeCN. The flask was then wrapped with parafilm and sonicated for 5 minutes. After cooling, the sides of the flask were washed with 1.0 mL of MeCN and the flask sonicated for an additional minute. The mixture was carefully diluted to the mark with acetonitrile. 1.0 mL of this solution was transferred by pipet to a 25-mL volumetric flask and diluted to the mark with the sample diluent from Step B.

Step D. Procedures

The HPLC system was equilibrated for at least 10 minutes at the mobile phase condition given in Step A. The standard preparation from Step C was injected twice, and the average area response for the 3-methylisoquinoline peaks should agree within ±1% of their average. The sample preparation was injected once.

Step E. Calculations

The concentration (mg/mL) of the MCPBA solution was calculated using the following equation:

$$\text{mg/mL of MCPBA solution} = (w - (A/As) \times Cs \times 250) \times \frac{172.57}{143.19}$$

where:

A=area response of the 3-methylisoquinoline for the Sample Solution

B=weight (mg) of the 3-methylisoquinoline in the Sample Preparation

As=average area response of the 3-methylisoquinoline for the Standard Solution

Cs=concentration of the 3-methylisoquinoline Standard Preparation

172.57=formula weight for 3-methylisoquinoline

143.19=formula weight for MCPBA

As an illustration of the assay, an MCPBA sample from Spectrum (Lot# LF0102, 72.7% MCPBA) was assayed, and a value of 72.8% (wt.%) for MCPBA was obtained.

EXAMPLE 2

Preparation of Omeprazole with Methylene Chloride as Solvent

A solution of potassium bicarbonate (14.0 g, 0.140 mol, 1.2 equivalents) in deionized water (115 mL) was added to a solution of pyrmetazole (0.114 mol) in methylene chloride (170 mL) in a one-liter, three-necked round-bottom flask, and the mixture was cooled to 0° C. A solution of meta-chloroperoxybenzoic acid (MCPBA) (28 g, 0.114 mol, 1.0 equivalent) in methylene chloride (51 mL) and ethanol (13.3 mL) was prepared and assayed by the 3-methylisoquinoline/HPLC procedure described in Example 1 to ensure that exactly one molar equivalent of MCPBA is used. The solution is then cooled between 0–5° C. and added, subsurfacely directed at the tip of the impeller, to the rapidly agitated solution of pyrmetazole over a 2-hour period. The oxidation conversion was 99.8% with no over-oxidation to sulfone or N-oxides, as determined by HPLC analysis. Cold deionized water (115 mL, 5° C.) and 50% NaOH (15 mL) were then added to the reaction mixture. The solution was allowed to stand at 0–5° C. for thirty minutes and the phases separated. The methylene chloride layer was discarded and the aqueous layer concentrated under vacuum (50 mm Hg) for 2 hours at 15° C. to remove the bulk of the residual methylene chloride. The ethanol level was then re-adjusted to 15% v/v. At this point the residual methylene chloride level was less than 200 p.p.m., as determined by gas-liquid chromatographic analysis.

The crude product was then isolated by reactive crystallization by subsurface addition of methyl formate. Approximately 40% of the methyl formate charge (approximately 6 mL) was added during the first thirty minutes to adjust the pH from about 13.5 to 10.8. The mixture was allowed to stand for about twenty minutes to allow the internal temperature to cool back down to approximately 20° C. The mixture was seeded with pure omeprazole (0.5 g), and the remainder of the methyl formate (approximately 9 mL) was added subsurfacely over a 7-hour period to a pH of 9.0. The crude product was filtered, washed with 0.1% ammonia-water (50 mL) followed by methanol (40 mL).

The crude product was dissolved in 1:1 methanol-water (270 mL) and 50% NaOH (4 mL) in a 500-mL, three-necked, round-bottomed flask at 20° C. The solution was then cooled to 0–5° C. and the pH adjusted from >11.0 to approximately 10.5 by subsurface addition of 25% acetic acid over a 30-minute period, maintaining the temperature at 5° C. The batch was seeded with pure omeprazole (0.5 g), and the subsurface addition of 25% acetic acid was continued over a 4-hour period until pH 9.0 was achieved. After thirty minutes, the resulting solid was filtered, washed with 1:1 methanol-water (30 mL), and finally with cold (5° C.) methanol (30 mL). Pure omeprazole (100% as determined by HPLC analysis) was obtained after vacuum drying (50 mm Hg, 30–35° C.). The overall yield was 92.7%. The residual methanol level was 10 ppm, as determined by gas-liquid chromatography, with no detectable levels of methylene chloride (detection limit of 3 p.p.m.).

EXAMPLE 3

Preparation of Omeprazole with Toluene as Solvent

A solution of potassium bicarbonate (14.0 g, 0.140 mol, 1.2 equivalents) in deionized water (115 mL) was added to a solution of pyrmetazole (0.114 mol) in toluene (310 mL) in a one-liter, three-necked round-bottom flask, and the mixture was cooled to 0° C. Following the bicarbonate addition, a solution of meta-chloroperoxybenzoic acid (0.114 mol, 1 equivalent) in toluene (53 mL) and ethanol (20 mL) was assayed and charged to the pyrmetazole solution as in Example 2. The oxidation conversion was 99.8% with no over-oxidation to sulfone or N-oxides. Cold deionized water (145 mL, 5° C.) and 50% NaOH (12 mL) were then added to the reaction mixture. The solution was allowed to stand at 0–5° C. for thirty minutes and the phases separated. The toluene layer was discarded and the aqueous layer concentrated under vacuum (50 mm Hg) for 2 hours at 15° C. to remove the bulk of the residual toluene. The ethanol level was then adjusted to 15% v/v. At this point the residual toluene level was less than 400 p.p.m., as determined by gas-liquid chromatographic analysis.

The crude product was then isolated by reactive crystallization by subsurface addition of methyl formate as in

Example 2. It was filtered, washed with 0.1% ammonia-water (50 mL) followed by methanol (40 mL). The wet crude product was then processed to pure omeprazole as in Example 2. The overall yield was 93.8% with an HPLC purity of 100%. The residual methanol level was 10 ppm, as determined by gas-liquid chromatography, with no detectable levels of toluene (detection limit 3 p.p.m).

EXAMPLE 4

A pharmaceutical composition containing omeprazole prepared according to the process of the present invention as the active ingredient is illustrated in the following formulation.

Capsules containing 30 mg of omeprazole of the present invention were prepared from the following ingredients:

Compound of Example 2 or 3	300 grams
Lactose	700 grams
Microcrystalline cellulose	40 grams
Hydroxypropyl cellulose, low-substituted	62 grams
Disodium hydrogenphosphate	2 grams
Purified water	q.s.

The omeprazole of Example 2 or 3 was mixed with the dry ingredients and granulated with a solution of disodium hydrogenphosphate. The wet mass was forced through an extruder and sphreronized and dried in a fluidized bed dryer.

500 Grams of the pellets were coated with a solution of hydroxypropyl methylcellulose (30 grams) in water (750 mL) using a fluidized bed coater. After drying, the pellets were coated with a second coating as follows:

Coating Solution:

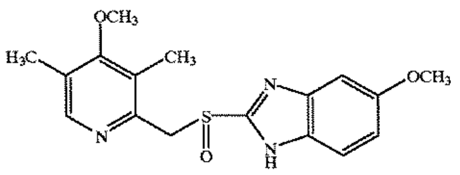
Hydroxypropyl methylcellulose phthalate	70 grams
Cetyl alcohol	4 grams
Acetone	200 grams
Ethanol	600 grams

The final coated pellets were filled into capsules.

What is claimed is:

1. A process for the preparation of omeprazole, having the formula I,

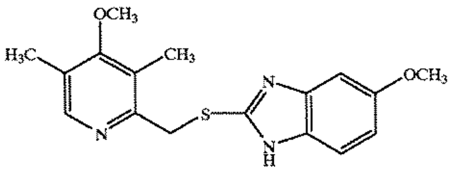
I



which comprises:

(a) treating, at about −5 to +5° C., a buffered solution of pyrmetazole, having the formula II, in a non-alcoholic organic

II



reaction solvent, with one equivalent, relative to the number of moles of said pyrmetazole, of meta-chloroperoxybenzoic dissolved in the non-alcoholic organic reaction solvent in admixture with an alcoholic solvent at about 0–5° C. followed by aging in the presence of an aqueous base;

(b) separating the aqueous phase of the aged reaction mixture from the organic phase; and

(c) removing residual non-alcoholic organic reaction solvent from said aqueous phase followed by re-adjusting the alcoholic solvent concentration to about 15% v/v.

2. The process according to claim **1** wherein the alcoholic solvent is selected from methanol, ethanol, isopropanol, and 1-butanol.

3. The process according to claim **2** wherein the alcoholic solvent is ethanol.

4. The process according to claim **1** which further comprises:

(a) crystallizing crude product from said aqueous phase by subsurface addition of a C_{1-3} alkyl formate to adjust the pH from about 13.5 to about 10.6–10.8, aging for about 10–20 minutes, allowing the temperature to reach about 20° C., seeding, and adding remainder of said alkyl formate over 6–8 hours to adjust the pH to about 9.0–9.3; and

(b) isolating crude product by filtration and washing with ammonia-water and methanol.

5. The process according to claim **4** which further comprises:

(a) recrystallizing crude product in methanol-water containing aqueous sodium hydroxide by cooling to about 0–5° C., adjusting the pH to about 10.5 by subsurface addition of 25% aqueous acetic acid, seeding, adding 25% aqueous acetic acid to a pH of about 9.0, and aging for about 0.5 hours; and

(b) isolating pure product by filtration, washing with methanol-water and cold methanol, and vacuum drying.

6. The process according to claim **1** wherein residual non-alcoholic organic reaction solvent is removed from the aqueous phase by vacuum distillation at about 25–70 mm Hg and about 15–35° C. for about 1–4 hours.

7. The process according to claim **1** wherein the non-alcoholic organic reaction solvent is selected from an aromatic hydrocarbon solvent and a chlorinated aliphatic hydrocarbon solvent.

8. The process according to claim **7** wherein the aromatic hydrocarbon solvent is toluene.

9. The process according to claim **7** wherein the chlorinated aliphatic hydrocarbon solvent is selected from methylene chloride, 1,2-dichloroethane, and chloroform.

10. The process according to claim **9** wherein the chlorinated aliphatic hydrocarbon solvent is methylene chloride.

11. The process according to claim **1** wherein the aging is allowed to proceed at about 0–5° C. for about 0.5–1.0 hours.

12. The process according to claim **1** wherein the buffer comprises aqueous sodium bicarbonate or aqueous potassium bicarbonate.

13. The process according to claim **1** wherein the aqueous base comprises aqueous sodium hydroxide or aqueous potassium hydroxide.

14. The process according to claim **4** wherein the C_{1-3} alkyl formate in Step (a) is methyl formate.

15. The process according to claim **5** wherein the volume ratio of methanol to water in Steps (a) and (b) is 2:1 to 0.5–1.

16. The process according to claim **15** wherein the volume ratio of methanol to water is 1:1.

17. The process according to claim **6** wherein the vacuum distillation is performed at a pressure of about 50 mm Hg and a temperature of about 15–25° C.

18. The process according to claim **4** wherein the concentration of ammonia-water in Step (b) is 0.01–1.0%(v/v).

19. The process according to claim **18** wherein the concentration of ammonia-water is 0.1%(v/v).

20. The process according to claim **1** wherein the molar amount of oxidizing agent to be added to said pyrmetazole solution is calculated by means of a high-performance liquid chromatographic assay which quantifies the extent of oxidation of an excess of 3-methylisoquinoline to 3-methylisoquinoline-N-oxide.

21. The process according to claim **1** wherein the oxidizing agent is added subsurfacely such that the solution enters the reaction mixture at the tip of the agitator blades.

22. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) obtained by the process of claim **5** containing less than 100 parts per million of residual aromatic hydrocarbon solvent.

23. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) obtained by the process of claim **5** containing less than 100 parts per million of residual chlorinated aliphatic hydrocarbon solvent.

24. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) according to claim **22** wherein the aromatic hydrocarbon solvent is toluene.

25. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) according to claim **23** wherein the chlorinated aliphatic hydrocarbon solvent is methylene chloride.

26. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) containing less than three parts per million of residual aromatic hydrocarbon solvent and 10–20 p.p.m. of residual methanol.

27. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) containing less than three parts per million of residual chlorinated aliphatic hydrocarbon solvent and 10–20 p.p.m. of residual methanol.

28. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) according to claim **26** wherein the aromatic hydrocarbon solvent is toluene.

29. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) according to claim **27** wherein the chlorinated aliphatic hydrocarbon solvent is methylene chloride.

* * * * *

EXHIBIT E

US006191148B1

(12) **United States Patent**
McManus et al.

(10) **Patent No.: US 6,191,148 B1**
(45) **Date of Patent: Feb. 20, 2001**

(54) **OMERAZOLE PROCESS AND COMPOSITIONS THEREOF**

(75) Inventors: **James W. McManus**; **Nick Anousis**; **Benjamin Newton Banks**, all of Albany, GA (US); **Hui Liu**, Greenbrook; **Lingwen Zhou**, North Brunswick, both of NJ (US)

(73) Assignee: **Merck & Co., Inc.**, Rahway, NJ (US)

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: **09/461,605**

(22) Filed: **Dec. 15, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/169,231, filed on Oct. 9, 1998.

(60) Provisional application No. 60/096,037, filed on Aug. 11, 1998.

(51) **Int. Cl.**[7] **A61K 31/4439**; C07D 401/12

(52) **U.S. Cl.** **514/341**; 546/273.7

(58) **Field of Search** 546/273.7; 514/341

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,255,431	3/1981	Junggren et al. .
5,386,032	1/1995	Brandstrom et al. .
5,391,752	2/1995	Hoerrner et al. .
5,635,520	6/1997	Uda .

FOREIGN PATENT DOCUMENTS

0 484 265 A1	5/1992	(EP) .
0 302 720 B1	11/1992	(EP) .
539793	1/1985	(ES) .
540147	2/1985	(ES) .
550070	12/1985	(ES) .
2239453	7/1991	(GB) .
WO98/09962	3/1998	(WO) .
WO98/40377	9/1998	(WO) .
WO98/40378	9/1998	(WO) .

Primary Examiner—Patricia L. Morris
(74) *Attorney, Agent, or Firm*—Philippe L. Durette; Melvin Winokur

(57) **ABSTRACT**

The present invention describes an improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole whereby the sulfide precursor pyrmetazole is reacted subsurfacely with exactly one molar equivalent of meta-chloroperoxybenzoic acid in a chlorinated aliphatic hydrocarbon or aromatic hydrocarbon solvent, such as methylene chloride or toluene; residual organic solvent is removed from the aqueous layer by vacuum distillation; crude product is obtained by reactive crystallization with an alkyl formate or formic acid solution and seeding; and pure product is isolated by recrystallization in methanol-water containing aqueous NaOH by subsurface addition of aqueous acetic acid to pH 9.0, seeding, filtration, washing, and drying. Omeprazole and compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent and diminished levels of alcoholic solvent are also described.

16 Claims, No Drawings

OMERAZOLE PROCESS AND COMPOSITIONS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation-in-part of application Ser. No. 09/169,231, filed Oct. 9, 1998, which is related to U.S. provisional application Serial No. 60/096,037, filed Aug. 11, 1998, the contents of both of which are hereby incorporated by reference.

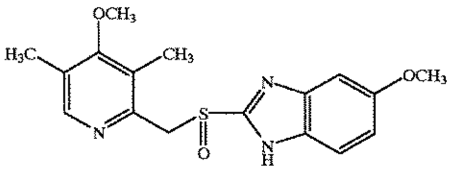
FIELD OF THE INVENTION

The present invention provides a novel improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole. Omeprazole and compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent and diminished levels of alcoholic solvent are also disclosed.

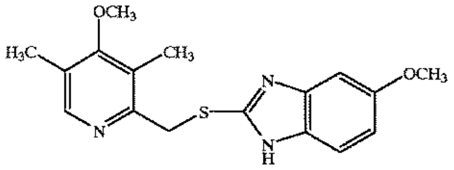
BACKGROUND OF THE INVENTION

Omeprazole, the generic name for 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (denoted as Formula I below) is a well-described gastric proton-pump inhibitor and is on the market as LOSEC® or PRILOSEC® for the treatment of gastric and duodenal ulcers, gastritis, duodenitis, and reflux esophagitis (see Merck Index, 12th Ed., entry 6977, and references cited therein). Omeprazole is commercially prepared via a multi-step sequence, the last step of which is oxidation of the sulfide intermediate, 5-methoxy-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thiol]-1H-benzimidazole (denoted as Formula II below), known generically as pyrmetazole, which is typically effected with a peroxy acid, such as meta-chloroperoxybenzoic acid (hereinafter referred to as MCPBA) (U.S. Pat. Nos. 4,255,431; 5,386,032; and EPO 484,265), magnesium monoperoxyphthalate (MMPP) (U.S. Pat. No. 5,391,752), or peroxyacetic acid (WO 98/09962), in a suitable non-alcoholic organic reaction solvent.

(I)



(II)



Oxidants other than peroxyacids have also been used for the oxidation of pyrmetazole to omeprazole. EPO 302,720 utilizes aqueous hydrogen peroxide in the presence of a vanadium catalyst, Spanish application No. ES 550,070 discloses periodate as the oxidant, and Spanish applications No. ES 539,793 and ES 540,147 describe iodosobenzene and 3-methyliodosobenzene, respectively. A photooxidative method is disclosed in GB 2,239,453.

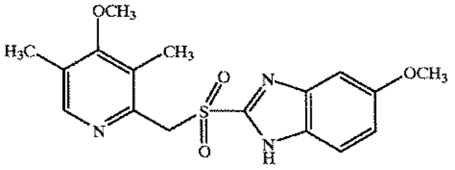
Reduction of omeprazole-N-oxide to omeprazole is described in WO 98/40377 and WO 98/40378.

The preferred oxidizing agent is usually MCPBA, and suitable non-alcoholic organic reaction solvents include aromatic hydrocarbon solvents, such as benzene and toluene or a mixture thereof, and chlorinated aliphatic hydrocarbon solvents, such as chloroform, 1,2-dichloroethane, and methylene chloride or a mixture thereof, in admixture with an alcoholic solvent, such as methanol, ethanol, isopropanol, or 1-butanol. The preferred non-alcoholic organic reaction solvent is usually chloroform, methylene chloride, or toluene, and the preferred alcoholic solvent is ethanol.

Prior processes to omeprazole have numerous disadvantages that limit both the yield and the purity of the final product.

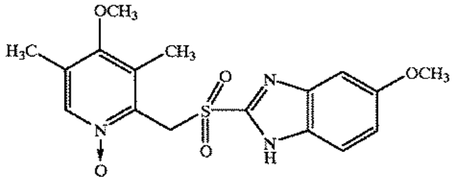
A significant drawback of such prior methods is incomplete oxidative conversion of pyrmetazole into omeprazole as well as over-oxidation. Two such by-products of over-oxidation are the sulfone of structural formula V and the sulfone-N-oxide of structural formula VI. Incomplete and over-oxidation, characteristic of the previous methods, arise from ineffective control over the amount of the oxidizing agent as well as the manner in which the oxidizing agent is charged into the reaction vessel. Prior methods do not use accurately determined amounts of the oxidizing agent and do not provide for careful control of its addition to the reaction mixture. Incomplete and over-oxidation both contribute to the presence of impurities and loss of yield of the final desired product.

(V)



5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridiny) methyl]sulfonyl]1H-benzimidazole[sulfone]

(VI)



5-Methoxy-2-[[(4-methoxy-3,5-dimethyl- 1-oxo-2-pyridinyl)methyl]sulfonyl]-1H-benzimidazole [sulfone-N-oxide]

Another disadvantage of prior procedures is the considerable loss of product in the purification and isolation steps due to solubility of omeprazole in the mother liquors and solvent washes.

A further drawback concerns diminished product quality resulting from occlusion of residual solvents and reaction by-products during the crystallization steps. It is desirable to eliminate residual levels of organic reaction solvent and recrystillization solvent impurities in the final crystalline product for toxicity/safety reasons.

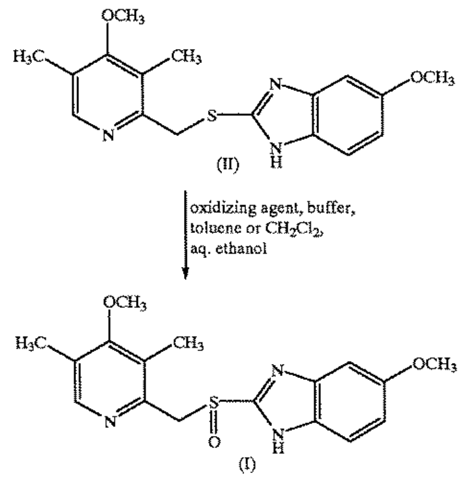
It is therefore an object of the present invention to provide an improved process for the preparation, purification, and isolation of omeprazole that overcomes the yield and product purity limitations of prior methods.

It is also an object of the invention to provide omeprazole and compositions of omeprazole having lower levels of residual non-alcoholic organic reaction solvent after the initial crude reactive crystallization step.

It is a further object of the present invention to provide omeprazole and compositions of omeprazole that contain no residual non-alcoholic organic reaction solvent within the limits of chromatographic detection and lower levels of residual alcoholic solvent.

SUMMARY OF THE INVENTION

The present invention provides an improved process for the preparation, purification, and isolation of omeprazole of the Formula 1. The last chemical transformation in the preparation of omeprazole is the oxidative conversion of the sulfide intermediate pyrmetazole of the Formula II into its sulfoxide derivative omeprazole of the Formula 1.



In one embodiment of the improved process, the oxidizing agent is meta-chloroperoxybenzoic acid (MCPBA), and the non-alcoholic organic reaction solvent is a chlorinated aliphatic hydrocarbon solvent or an aromatic hydrocarbon solvent in admixture with an alcoholic solvent, such as methanol, ethanol, isopropanol, or 1-butanol, in particular, ethanol. In a class of this embodiment, the chlorinated aliphatic hydrocarbon solvent is chloroform, 1,2-dichloroethane, or methylene chloride or a mixture thereof, and the aromatic hydrocarbon solvent is benzene or toluene or a mixture thereof. In a subclass of this class, the chlorinated aliphatic hydrocarbon solvent is methylene chloride, and the aromatic hydrocarbon solvent is toluene. In this embodiment, oxidative conversion of pyrmetazole to omeprazole has been optimized by careful control of the amount of MCPBA charged to the reaction vessel. The use of one molar equivalent of MCPBA relative to the number of moles of pyrmetazole minimizes over-oxidation to the sulfone V and sulfone-N-oxide VI, and incomplete reaction to give back pyrmetazole II, resulting in fewer impurities and higher yields. In another embodiment of the present invention, the concentration of MCPBA in the charging solution is calculated using a novel analytical method based upon MCPBA oxidation of 3-methylisoquinoline to its N-oxide derivative and subsequent HPLC quantitation. Without this assay there exists no practical way to avoid either over-oxidation or incomplete conversion of pyrmetazole into omeprazole.

In a further embodiment of the present invention, control over localized over-oxidation is achieved by subsurface addition of MCPBA, providing for entry of the oxidizing solution into the reaction vessel slightly above the agitator blades and directed perpendicular to the flow from the impeller, with simultaneous control of the reaction temperature. Incorporation of these novel features into the process ensures complete conversion of pyrmetazole into omeprazole with minimal formation of over-oxidized by-products V and VI.

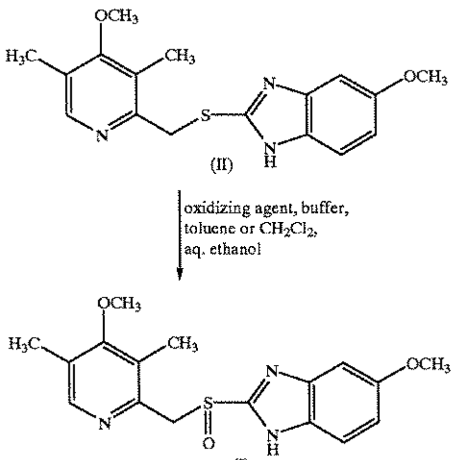
In another embodiment of the present invention, the isolation of the crude product has been improved by vacuum distillation of the crude aqueous phase after extraction of the reaction mixture prior to crystallization to remove most of the entrained chlorinated aliphatic hydrocarbon solvent or aromatic hydrocarbon solvent from the oxidation step. The concentration of the alcoholic solvent, in particular ethanol, is then re-adjusted in order to promote good crystal growth during the crude crystallization step. The crystallization step involves a two-stage neutralization with a C_{1-3} alkyl formate, preferably methyl formate, or a solution of formic acid in aqueous methanol or ethanol, which is added subsurfacely through a diptube slightly above the agitator blades and directed perpendicular to the flow from the impeller. This mode of addition of the methyl formate or formic acid solution ensures rapid dispersion of the neutralizing agent, which promotes crystal growth over spontaneous nucleation. In so doing, occlusion of mother liquors in the crystals is minimized. Lowering the concentration of ammonia, relative to that used in prior procedures, in the ammonia-water wash, necessary to remove color impurities in the crude product, provides for further improvement in the yield of omeprazole.

A further embodiment of the present invention concerns the final purification step. A methanol-water mixture is used for the crystallization step which is initiated by subsurface addition of aqueous acetic acid and subsequent seeding with omeprazole. The same methanol-water mixture is employed as a displacement wash to remove mother liquors and dissolved impurities while suppressing solubility losses. In this fashion, significant yield improvements are obtained with no adverse impact on product quality.

Crystalline omeprazole is thus obtained with significant improvement in yield and purity. The isolated material contains no chromatographically detectable levels of residual non-alcoholic organic reaction solvent and ethanol, and less than 30 p.p.m. of residual methanol.

DETAILED DESCRIPTION OF THE INVENTION

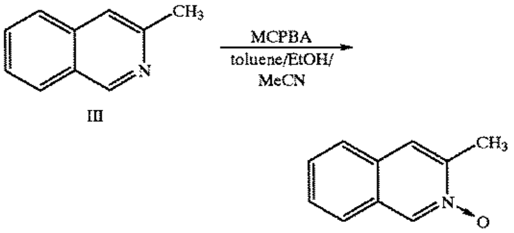
The instant invention relates to an improved process for the preparation, purification, and isolation of the proton-pump inhibitor omeprazole and to novel compositions thereof. Omeprazole, having formula I, is prepared by reacting a solution of pyrmetazole, having Formula II, cooled to about −5 to +5° C. and buffered to a pH of about 6 to 8, with one molar equivalent of an oxidizing agent, relative to the number of moles of pyrmetazole, dissolved in a non-alcoholic organic reaction solvent in admixture with an alcoholic solvent. The alcoholic solvent is selected from methanol, ethanol, isopropanol, and 1-butanol.



(II)

(I)

In one embodiment of the instant improved process, the buffered solution comprises potassium bicarbonate, the oxidizing agent is meta-chloroperoxybenzoic acid, and the non-alcoholic organic reaction solvent is chloroform, methylene chloride, or a mixture thereof, or toluene, in admixture with ethanol. The reaction is carried out such that both the completeness and the extent of the oxidation are optimized. To force the reaction to proceed in a near quantitative fashion, it is necessary that any excess of the oxidizing agent, MCPBA, be minimized. Hence, the solution containing the oxidizing agent is accurately assayed so that an exact amount of reagent will be charged to the reaction vessel. In prior methods, the amount of MCPBA added was based on the commercial supplier's assay number. Since MCPBA solid contains about 15–25% water for safety reasons, the solid is not homogeneous. Therefore, the manufacturer can provide only the average assay results of MCPBA. If MCPBA from different containers and different suppliers is used, an inaccurate charge of MCPBA will result. A novel analytical method has therefore been developed to quantify MCPBA in the charging solution in order to deliver an accurate amount of the oxidizing agent. According to the assay, an excess amount of 3-methylisoquinoline (III) is reacted with MCPBA in toluene/ethanol solution to form 3-methylisoquinoline N-oxide (IV), according to the equation:



III

IV

The reaction is fast and quantitative. The remaining tertiary amine in the reaction mixture is quantitated by reverse-phase high-performance liquid chromatography (RP-HPLC). The amount of the amine consumed during the reaction is used to calculate the concentration of the MCPBA solution.

It is also important that no excess oxidizing agent accumulate during addition of the reagent. This is best accomplished by subsurface addition of MCPBA, such that the solution enters the batch through a diptube slightly above the agitator blades and directed perpendicular to the flow from the impeller. This mode of addition provides for immediate dispersion of the oxidant, thus limiting localized over-oxidation.

Completeness and extent of oxidation are also enhanced by controlling the reaction temperature without crystallization of the oxidizing agent. The optimum temperature range is about 0–5° C. for the solution of the oxidizing agent and about −5 to +5° C. for the reaction mixture throughout the addition process. Higher temperatures of either the MCPBA solution or the reaction mixture will result in some formation of sulfone V and sulfone-N-oxide VI. Likewise, much lower temperatures temporarily suppress the oxidation reaction, which results in a localized accumulation of the oxidizing agent that can lead to over-oxidation products.

After addition of the solution containing the oxidizing agent, aqueous base, for example 50% NaOH or KOH, is added, the solution allowed to age for about 0.5–1.0 hours at 0–5° C., and the aqueous phase separated from the organic phase. To minimize residual levels of the non-alcoholic organic reaction solvent, in particular toluene, chloroform, or methylene chloride, in the crude product, which translates into higher levels of volatile non-alcoholic organic reaction solvent in the pure product, it is important to remove as much entrained toluene, chloroform, or methylene chloride as possible from the crude aqueous phase. The source of residual toluene, chloroform, or methylene chloride is an emulsion that forms when the crude batch is extracted from toluene, chloroform, or methylene chloride with aqueous base. Removal of residual solvent may be accomplished by vacuum distillation of the aqueous phase at a pressure of about 25–70 mm Hg and temperature of about 15–35° C. for about 1–4 hours. In further exemplification, the distillation is carried out at about 50 mm Hg and about 15° C. for 2 hours. The vacuum distillation procedure reduces the pre-crystallization levels of toluene, chloroform, or methylene chloride to less than 400 p.p.m. Other options to break up the emulsion and effect better phase separation are less effective; these include filtration of the crude aqueous phase through a bed of Celite™, increasing the settling time, and addition of a strong electrolyte.

Since the distillation process also results in removal of the alcohol, in particular ethanol, its concentration must be re-adjusted to approximately 15%, in order to facilitate crystal growth during the crude crystallization process. A lower level of the alcoholic solvent, in particular ethanol, produces finer crystals which are more likely to dissolve during subsequent washes thereby diminishing yields of the crude product.

At this point, the reactive crystallization of omeprazole is initiated and maintained under controlled conditions. Approximately 40% of a C_{1-3}-alkyl formate charge, preferably methyl formate, is added over the first 30 minutes to bring the batch from a pH of about 13.5 to near supersaturation at a pH of about 10.6 to 10.8. The methyl formate addition is accomplished through a diptube which is narrowed at one end to create a fine stream and located slightly above the agitator blades and directed perpendicular to the flow from the impeller. This technique ensures rapid dispersion of the methyl formate so that occlusion of impurities is minimized. When a pH of about 10.6–10.8 is attained, the methyl formate addition is discontinued, and the batch is aged for ten to twenty minutes to allow the temperature to cool to approximately 20° C. prior to seeding. It is important to seed between pH 10.6 and 10.8. Below 10.6 spontaneous nucleation will occur with little crystal growth, if a sufficient seed bed is not present. Seeding is effected with pure, milled omeprazole (100% by HPLC), and the rest of the methyl formate is added subsurfacely over 6–8 hours to adjust the pH to about 9.0–9.3. This crystallization procedure improves both the yield and purity of the product. Without being held to a specific mechanism, it is believed that the purity enhancement is mainly due to preventing occlusion of mother liquors by promoting crystal growth over nucleation. Crude omeprazole at this stage contains less than 100 p.p.m. of residual toluene, chloroform, or methylene chloride, as determined by gas-liquid chromatographic analysis.

Reactive crystallization of crude omeprazole may also be carried out by neutralization of the aqueous basic solution of omeprazole with a solution of formic acid in aqueous methanol or ethanol, preferably a solution of 20% (v/v) formic acid in about 25% aqueous methanol, which is added in a subsurface manner as described in the previous paragraph. Enough formic acid solution is added in this fashion to adjust the pH from about 13.5 to near supersaturation at a pH of about 10.6 to 10.8. At this stage, seeding is effected with pure, milled omeprazole (100% by HPLC), and the rest of the formic acid solution is added subsurfacely over 6–8 hours to adjust the pH to about 9.0–9.3. This alternative neutralization procedure with formic acid solution in place of methyl formate produces crude crystalline omeprazole with larger, more uniform crystals. The average particle size of the omeprazole crystals obtained with formic acid neutralization is approximately 280 μm as contrasted to an average particle size of 180 μm obtained with methyl formate neutralization. The larger particle size translates into more efficient centrifugation or filtration leading to significantly enhanced productivity on a production scale.

The crude crystallized product is then filtered, washed with 0.01–1.0%, preferably 0.1%, ammonia-water, and then methanol.

The crude wet omeprazole is then purified by dissolving it in 2:1–0.5-(v/v) methanol-water solution containing aqueous base, preferably 50% NaOH or KOH, at 20° C., cooling the basic solution to about 0–5° C., reducing the pH from >11.0 to approximately 10.5 by subsurface addition through a narrowed end diptube (configuration of apparatus same as in crude isolation step) of aqueous acetic acid, preferably 25% aqueous acetic acid, over a 30-minute period, while maintaining the temperature at 0–5° C. At this point the batch is seeded with pure omeprazole (100% by HPLC), and the subsurface addition of 25% aqueous acetic acid is continued over a 2–4 hour period until a pH of about 9.0 is attained. The batch is then aged for 0.5–1.0, preferably 0.5 hours. Following the aging period, the product is filtered, washed with the same methanol-water mixture to displace the mother liquors containing the impurities, and finally with cold methanol. Pure omeprazole is obtained after vacuum drying with a nitrogen purge at 30–50 mm Hg and 30–35° C.

In one embodiment of the present invention, the methanol-water ratio in this final purification step is 1:1. Previous methods used a higher methanol to water ratio. Lowering the proportion of methanol in the solvent mixture used in the displacement wash minimizes solubility losses and provides the purification demands, thereby improving the yield of the final product without compromising product quality.

Crystalline omeprazole obtained using the improved process of the instant invention has an HPLC purity of greater than 99.94% (area percentage) with no detectable levels of residual toluene, chloroform, or methylene chloride, or a mixture thereof, entrained from the crude step as measured by gas-liquid chromatography, the detection limit being 3 p.p.m. Prior methods have afforded omeprazole containing 30–100 p.p.m. of residual non-alcoholic organic reaction solvent, namely toluene, chloroform, or methylene chloride. The pure product also contains less than 30 p.p.m. of methanol and no detectable levels of ethanol as measured by gas-liquid chromatography, the detection limit being 3 p.p.m. In one embodiment of the present invention, none of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole(pyrmetazole); 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfonyl]-1H-benzimidazole (sulfone V); and 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-1-oxo-2-pyridinyl)methyl]sulfonyl]-1H-benzimidazole(sulfone-N-oxide VI) is present to an extent greater than 0.04%.

For the preparation of pharmaceutical compositions in the form of dosage units for oral administration, omeprazole prepared according to the process of the present invention may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as an antifriction agent such as magnesium stearate, calcium stearate, and polyethyleneglycol waxes. The mixture is then pressed into tablets. If coated tablets are desired, the above-prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide, or with a lacquer dissolved in volatile organic solvent or mixture of solvents. To this coating various dyes may be added in order to distinguish among tablets with different amounts of active compound present.

Soft gelatin capsules may be prepared which contain a mixture of pure omeprazole prepared according to the process of the present invention and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin.

Pharmaceutical tablets for oral use are prepared in the following manner. The solid substances are ground or sieved to a certain particle size, and the binding agent is homogenized and suspended in a suitable solvent. The solid omeprazole prepared according to the process of the present invention and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension having the consistency of wet snow. The moistening causes the particles to aggregate slightly, and the resulting mass is pressed through a stainless steel sieve having a mesh size of about 1 millimeter. The layers of the mixture are dried in carefully controlled drying cabinets for approximately ten hours to obtain the desired particle size and consistency. The granules of the dried mixture are sieved to remove any powder. To this mixture, disintegrating, antifriction, and antiadhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The pressure applied affects the size of the tablet, its strength and ability to dissolve in water. The compression pressure used should be in the range of 0.5 to 5 tons. The tablets, especially those which are rough or bitter, may be coated with a layer of sugar or some other palatable substance. They are then packaged by machines having electronic counting devices.

The following examples illustrate the process of the present invention and are not intended to limit the scope of the invention set forth in the claims appended thereto.

EXAMPLE 1

HPLC Assay of MCPBA Charging Solution

Step A

HPLC Operating Parameters

High-performance liquid chromatography was performed using a Waters μBondapak C-18 column (4.6x300 mm, 10 μm particle size) with the following additional parameters:

Mobile phase: A=acetonitrile; B=0.1% H_3PO_4

Mode: isocratic 25% A/75% B at a flow rate of 1.0 mL/min

Injection size: 10 μL

Detector wavelength: 254 nm

Run time: 32 min.

Method of quantitation: Area by electronic integration

Approximate retention times:

3-methylisoquinoline: 3.5 mins.

3-methylisoquinoline N-oxide: 5.7 mins.

MCPBA: 11.4 mins.

Toluene: 25.1 mins.

Step B

Reagents

Acetonitrille (MeCN): HPLC Grade

Water: HPLC Grade

Phosphoric Acid: HPLC Grade

3-Methylisoquinoline: 98%

Sample Diluent: 50/50 (MeCN/0.1% H_3PO_4)

Step C

Preparation of 3-Methylisoquinoline Standard

20±5 mg of 3-methylisoquinoline (98%) was transferred into a 10 mL volumetric flask and dissolved in 1.0 mL of MeCN. 1.0 mL of MCPBA after warming to room temperature was carefully pipetted into the flask, and the sides of the flask were washed with 1.0 mL of MeCN. The flask was then wrapped with parafilm and sonicated for 5 minutes. After cooling, the sides of the flask were washed with 1.0 mL of MeCN and the flask sonicated for an additional minute. The mixture was carefully diluted to the mark with acetonitrile. 1.0 mL of this solution was transferred by pipet to a 25-mL volumetric flask and diluted to the mark with the sample diluent from Step B.

Step D

Procedures

The HPLC system was equilibrated for at least 10 minutes at the mobile phase condition given in Step A. The standard preparation from Step C was injected twice, and the average area response for the 3-methylisoquinoline peaks should agree within ±1% of their average. The sample preparation was injected once.

Step E

Calculations

The concentration (mg/mL) of the MCPBA solution was calculated using, the following equation:

$$\text{mg/ml of MCPBAP solution}=(B-(A/As)\times Cs\times 250)\times 172.57/143.19$$

where:

A=area response of the 3-methylisoquinoline for the Sample Solution

B=weight (mg) of the 3-methylisoquinoline in the Sample Preparation

As=average area response of the 3-methylisoquinoline for the Standard Solution

Cs=concentration of the 3-methylisoquinoline Standard Preparation

172.57=formula weight for 3-methylisoquinoline

143.19=formula weight for MCPBA

As an illustration of the assay, an MCPBA sample from Spectrum (Lot# LF0102, 72.7% MCPBA) was assayed, and a value of 72.8% (wt. %) for MCPBA was obtained.

EXAMPLE 2

Preparation of Omeprazole With Methylene Chloride as Solvent

A solution of potassium bicarbonate (14.0 g, 0.140 mol, 1.2 equivalents) in deionized water (115 mL) was added to a solution of pyrmetazole (0.114 mol) in methylene chloride (170 mL) in a one-liter, three-necked round-bottom flask, and the mixture was cooled to 0° C. A solution of meta-chloroperoxybenzoic acid (MCPBA) (28 g, 0.114 mol, 1.0 equivalent) in methylene chloride (51 mL) and ethanol (13.3 mL) was prepared and assayed by the 3-methylisoquinoline/HPLC procedure described in Example 1 to ensure that exactly one molar equivalent of MCPBA is used. The solution is then cooled between 0–5° C. and added, subsurfacely directed at the tip of the impeller, to the rapidly agitated solution of pyrmetazole over a 2-hour period. The oxidation conversion was 99.8% with no over-oxidation to sulfone or N-oxides, as determined by HPLC analysis. Cold deionized water (115 mL, 5° C.) and 50% NaOH (15 mL) were then added to the reaction mixture. The solution was allowed to stand at 0–5° C. for thirty minutes and the phases separated. The methylene chloride layer was discarded and the aqueous layer concentrated under vacuum (50 mm Hg) for 2 hours at 15° C. to remove the bulk of the residual methylene chloride. The ethanol level was then re-adjusted to 15% v/v. At this point the residual methylene chloride level was less than 200 p.p.m., as determined by gas-liquid chromatographic analysis.

The crude product was then isolated by reactive crystallization by subsurface addition of methyl formate. Approximately 40% of the methyl formate charge (approximately 6 mL) was added during the first thirty minutes to adjust the pH from about 13.5 to 10.8. The mixture was allowed to stand for about twenty minutes to allow the internal temperature to cool back down to approximately 20° C. The mixture was seeded with pure omeprazole (0.5 g), and the remainder of the methyl formate (approximately 9 mL) was added subsurfacely over a 7-hour period to a pH of 9.0. The crude product was filtered, washed with 0.1% ammonia-water (50 mL) followed by methanol (40 mL).

The crude product was dissolved in 1:1 methanol-water (270 mL) and 50% NaOH (4 mL) in a 500-mL, three-necked, round-bottomed flask at 20° C. The solution was then cooled to 0–5° C. and the pH adjusted from >11.0 to approximately 10.5 by subsurface addition of 25% acetic acid over a 30-minute period, maintaining the temperature at 5° C. The batch was seeded with pure omeprazole (0.5 g), and the subsurface addition of 25% acetic acid was continued over a 4-hour period until pH 9.0 was achieved. After thirty minutes, the resulting solid was filtered, washed with 1:1 methanol-water (30 mL), and finally with cold (5° C.) methanol (30 mL). Omeprazole was obtained after vacuum drying (50 mm Hg, 30–35° C.). The overall yield was 92.7%. The residual methanol level was 10 ppm, as determined by gas-liquid chromatography, with no detectable levels of methylene chloride and ethanol (detection limit of 3 p.p.m.). The HPLC purity profile (area percentage) of the isolated omeprazole was found to be:

Omeprazole (I): 99.937

Pyrmetazole (II): 0.022

Sulfone N-oxide (VI): 0.031

Sulfone (V): 0.010

using the following HPLC conditions:

Reagents and Solutions:

Methanol: HPLC Grade

Acetonitrile: HPLC Grade

Water: HPLC Grade

Disodium Hydrogen Phosphate (Na_2HPO_4 anhydrous): HPLC Grade

Sodium Dihydrogen Phosphate ($NaH_2PO_4.H_2O$): HPLC Grade

0.5 M Disodium Hydrogen Phosphate (Na_2HPO_4 anhydrous) Solution—Dissolve 71.0 grams of Disodium Hydrogen Phosphate in 1 liter of water.

1.0 M Sodium Dihydrogen Phosphate ($NaH_2PO_4.H_2O$) Solution—Dissolve 138.0 grams of Sodium Dihydrogen Phosphate in 1liter of water.

pH 7.6 Phosphate Buffer Solution—Transfer 6.5 ml of the 1.0 M Sodium Dihydrogen Phosphate ($NaH_2PO_4.H_2O$) solution and 79.0 ml of the 0.5 M Disodium Hydrogen Phosphate (Na_2HPO_4 anhydrous) solution to a 5 liter (5000 ml) bottle and dilute to volume with water. Adjust pH to 7.6±0.1 with phosphoric acid if necessary. Note: If the pH is not accurate, the retention time of the pyrmetazole will be directly affected.

Sample Prep:

30–35 mg omeprazole is dissolved in 100 ml MeOH.

Chromatographic Conditions:

Column: Lichrospher RP 8.5, 5 micron, 12.5 cm ×4.0 mm.

Mobile Phase: A) MeCN and B) phosphate buffer (ionic strength 0.025 at pH=7.6).

Mode: isocratic 30/70 A/B.

Flow rate: 1.5 mL/min.

Detector: photodiode array detector at 280 nm, bandwidth 32 nm, slit set to 16.

Run time: 20.0 mins.

Method of quantitation: Area by electronic integration.

Relative Retention Times:

Sulfone N-oxide (VI): 0.45 RRT

Sulfone (V): 0.65 RRT

Omeprazole (I): 1.00 RRT

Pyrmetazole (II): 3.67 RRT

EXAMPLE 3

Preparation of Omeprazole With Toluene as Solvent

A solution of potassium bicarbonate (14.0 g, 0.140 mol, 1.2 equivalents) in deionized water (115 mL) was added to a solution of pyrmetazole (0.114 mol) in toluene (310 mL) in a one-liter, three-necked round-bottom flask, and the mixture was cooled to 0° C. Following the bicarbonate addition, a solution of meta-chloroperoxybenzoic acid (0.114 mol, 1 equivalent) in toluene (53 mL) and ethanol (20 mL) was assayed and charged to the pyrmetazole solution as in Example 2. The oxidation conversion was 99.8% with no over-oxidation to sulfone or N-oxides. Cold deionized water (145 mL, 5° C.) and 50% NaOH (12 mL) were then added to the reaction mixture. The solution was allowed to stand at 0–5° C. for thirty minutes and the phases separated. The toluene layer was discarded and the aqueous layer concentrated under vacuum (50 mm Hg) for 2 hours at 15° C. to remove the bulk of the residual toluene. The ethanol level was then adjusted to 15% v/v. At this point the residual toluene level was less than 400 p.p.m., as determined by gas-liquid chromatographic analysis.

The crude product was then isolated by reactive crystallization by subsurface addition of methyl formate as in Example 2. It was filtered, washed with 0.1% ammonia-water (50 mL) followed by methanol (40 mL). The wet crude product was then processed to pure omeprazole as in Example 2. The overall yield was 93.8%. The residual methanol level was 10 ppm, as determined by gas-liquid chromatography, with no detectable levels of toluene and ethanol (detection limit 3 p.p.m). The HPLC purity profile (area percentage) of the isolated omeprazole was determined using the HPLC conditions given in Example 2 and found to be as follows:

Omeprazole (1): 99.969

Pyrmetazole (II): 0

Sulfone N-oxide (VI): 0.021

Sulfone (V): 0.010

The HPLC purity profile of isolated omeprazole prepared according to the procedures of Examples 2, 3, or 4 in three additional separate experiments were as follows:

Omeprazole	Pyrmetazole	Sulfone	Sulfone-N-oxide
99.941	0.0268	0.0085	0.024
99.964	0.0076	0.0046	0.024
99.924	0.0229	0.0132	0.040

EXAMPLE 4

Isolation of Crude Omeprazole by Reactive Crystallization With Formic Acid

The aqueous basic solution of omeprazole was prepared exactly as in Example 2 or 3 to the point of crystallization of the crude product. A solution of formic acid, methanol, and water in the ratio of 20:20:60 was then added to the aqueous solution of crude product in a subsurface manner at ambient temperature to effect crystallization. Approximately 40% of the formic acid solution was added over the first 30 minutes to adjust the pH from about 13.5 to about 10.8. The batch was then seeded with pure omeprazole (0.5 g), and the remainder of the formic acid solution was added subsurfacely over a seven-hour period to a pH of 9.0. The crude product was then filtered, washed with 0.1% ammonia-water (50 mL at 20° C.) followed by methanol (40 mL at 5° C.) and vacuum dried (50 mm Hg, 30–35° C.). The yield of the crude step was 95.4% with a purity of 99.9% (HPLC area percentage) and a median particle size of 285 μm.

EXAMPLE 5

A pharmaceutical composition containing omeprazole prepared according to the process of the present invention as the active ingredient is illustrated in the following formulation.

Capsules containing 30 mg of omeprazole of the present invention were prepared from the following ingredients:

Compound of Example 2, 3, or 4	300 grams
Lactose	700 grams
Microcrystalline cellulose	40 grams
Hydroxypropyl cellulose, low-substituted	62 grams
Disodium hydrogenphosphate	2 grams
Purified water	q.s.

The omeprazole of Example 2, 3, or 4 was mixed with the dry ingredients and granulated with a solution of disodium hydrogenphosphate. The wet mass was forced through an extruder and sphreronized and dried in a fluidized bed dryer. 500 Grams of the pellets were coated with a solution of hydroxypropyl methylcellulose (30 grams) in water (750 mL) using a fluidized bed coater. After drying, the pellets were coated with a second coating as follows:

Coating solution:

Hydroxypropyl methylcellulose phthalate	70 grams
Cetyl alcohol	4 grams
Acetone	200 grams
Ethanol	600 grams

The final coated pellets were filled into capsules.

What is claimed is:

1. 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole(omeprazole) of greater than 99.94% purity as determined by high-performance liquid chromatography and having less than 500 parts per million (p.p.m.) of residual ethanol relative to omeprazole.

2. Omeprazole according to claim **1** having less than 50 p.p.m. of residual ethanol relative to omeprazole.

3. Omeprazole according to claim **1** having less than 3 p.p.m. of residual ethanol relative to omeprazole.

4. Omeprazole according to claim **1** wherein none of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]thio]-1H-benzimidazole (pyrmetazole); 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfonyl]-1H-benzimidazole; and 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-1-oxo-2-pyridinyl)methyl]sulfonyl]-1H-benzimidazole is present to an extent greater than 0.04%.

5. Omeprazole according to claim **1** further characterized by having less than 3 p.p.m. of residual chloroform or methylene chloride or a mixture thereof relative to omeprazole.

6. Omeprazole according to claim **5** further characterized by having less than 30 p.p.m. of residual methanol relative to omeprazole.

7. Omeprazole according to claim **1** further characterized by having less than 3 p.p.m. of residual toluene relative to omeprazole.

8. Omeprazole according to claim **7** further characterized by having less than 30 p.p.m. of residual methanol relative to omeprazole.

9. Omeprazole according to claim **6** containing less than 3 p.p.m. of residual chlorinated aliphatic hydrocarbon solvent relative to omeprazole.

10. Omeprazole according to claim **8** containing less than 3 p.p.m. of residual aromatic hydrocarbon solvent relative to omeprazole.

11. A composition comprising omeprazole according to claim **1**.

12. The composition according to claim **11** wherein the omeprazole is further characterized by having less than 3 p.p.m. of residual toluene and less than 30 p.p.m. of residual methanol relative to omeprazole.

13. The composition according to claim **11** wherein the omeprazole is further characterized by having less than 3 p.p.m. of residual chloroform or methylene chloride or a mixture thereof and less than 30 p.p.m. of residual methanol relative to omeprazole.

14. A pharmaceutical composition comprising omeprazole according to claim **1** and a pharmaceutically acceptable excipient.

15. The pharmaceutical composition of claim **14** wherein the omeprazole is further characterized by having less than 3 p.p.m. of residual toluene and less than 30 p.p.m. of residual methanol relative to omeprazole.

16. The pharmaceutical composition of claim **14** wherein the omeprazole is further characterized by having less than 3 p.p.m. of residual chloroform or methylene chloride or a mixture thereof and less than 30 p.p.m. of residual methanol relative to omeprazole.

* * * * *

EXHIBIT F

US006428810B1

(12) **United States Patent**
Bergstrand et al.

(10) **Patent No.: US 6,428,810 B1**
(45) **Date of Patent: Aug. 6, 2002**

(54) **PHARMACEUTICAL FORMULATION COMPRISING OMEPRAZOLE**

(75) Inventors: **Pontus Bergstrand**, Gothenburg; **Peter Wang**, Mölndal, both of (SE)

(73) Assignee: **AstraZeneca AB**, Sodertalje (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/485,218**

(22) PCT Filed: **Nov. 3, 1999**

(86) PCT No.: **PCT/SE99/01989**

§ 371 (c)(1),
(2), (4) Date: **Feb. 4, 2000**

(87) PCT Pub. No.: **WO00/27366**

PCT Pub. Date: **May 18, 2000**

(30) **Foreign Application Priority Data**

Nov. 5, 1998 (SE) 9803772

(51) **Int. Cl.**[7] **A61K 9/36**; A61K 9/20

(52) **U.S. Cl.** **424/480**; 424/464; 424/468; 424/472; 424/474

(58) **Field of Search** 424/464, 465, 424/467, 468, 469, 470, 480, 489; 514/960, 965

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,690,960 A	* 11/1997	Bengtsson et al.	....	424/480
5,817,338 A	* 10/1998	Bergstrand et al.	....	424/468
6,090,827 A	7/2000	Erickson et al.	....	514/338

FOREIGN PATENT DOCUMENTS

EP	0005129	10/1979
EP	0124495	11/1984
EP	0247983	12/1987
EP	0496437	7/1992
WO	9427988	12/1994
WO	9501977	1/1995
WO	9601623	1/1996
WO	9725066	7/1997

OTHER PUBLICATIONS

Pilbrant, A. et al., "Development of an oral formulation of omeprazole", *Scand. J. Gastroenterol*, 1985; 20 (suppl): 113–120.

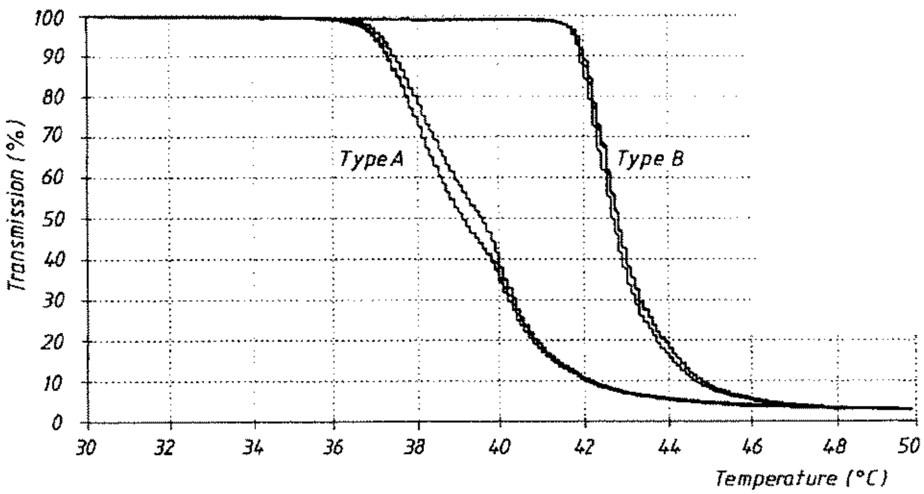
* cited by examiner

Primary Examiner—Thurman K. Page
Assistant Examiner—Charesse L. Evans
(74) *Attorney, Agent, or Firm*—White & Case LLP

(57) **ABSTRACT**

An enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, one of the single enantiomers of omeprazole and an alkaline salt of one of the single enantiomers of omeprazole, wherein the formulation comprises a core material that comprises the active ingredient and optionally an alkaline reacting compound, the active ingredient is in admixture with a pharmaceutically acceptable excipient, such as for instance a binding agent, and on said core material a separating layer and an enteric coating layer. A hydroxypropyl cellulose (HPC) with a specific cloud point is used in the manufacture of the claimed pharmaceutical formulations. Furthermore, the application describes the processes for their preparation and the use of the claimed formulations in medicine.

22 Claims, 4 Drawing Sheets



Cloud point determinations of the two different qualities of HPC named Type A and Type B (according to Example 3).

Fig. 1

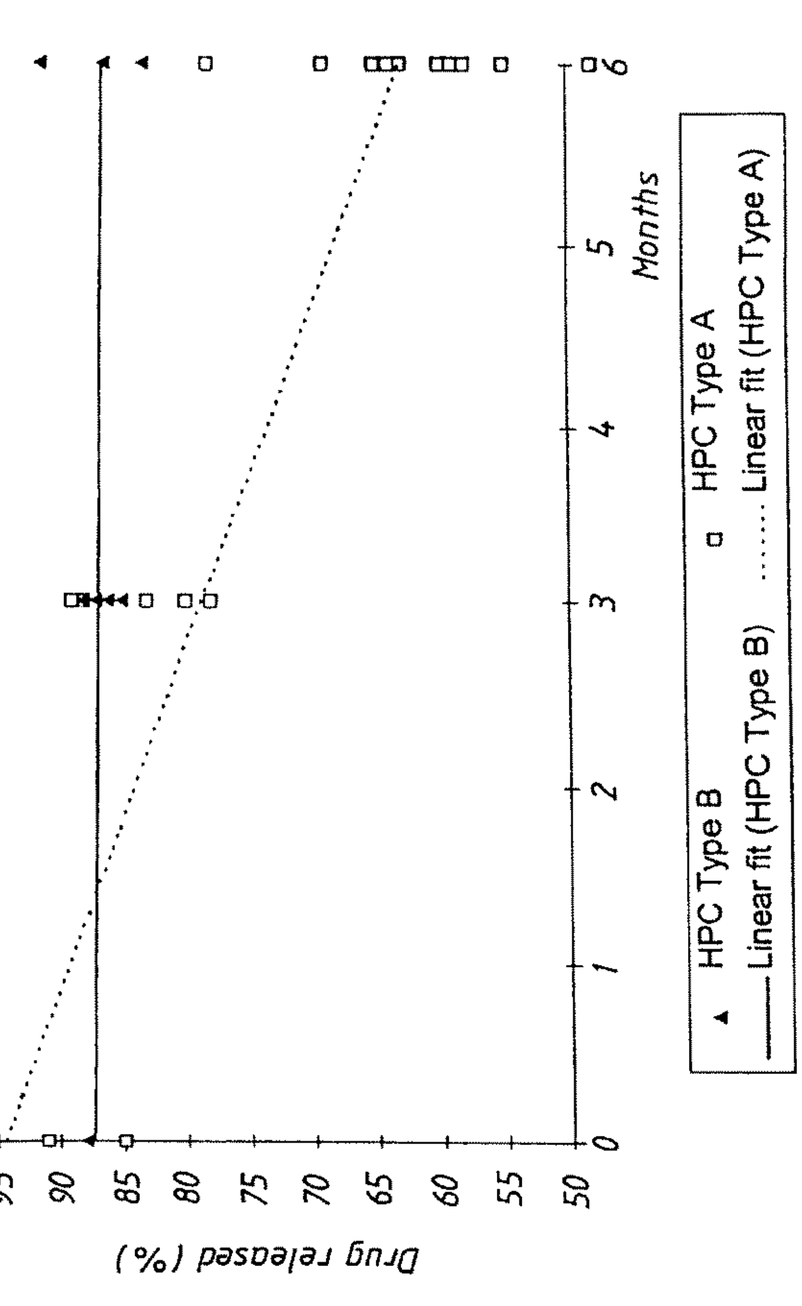

Drug released (%)
100
95
90
85
80
75
70
65
60
55
50
0
1
2
3
4
5
6
Months
HPC Type B
Linear fit (HPC Type B)
HPC Type A
Linear fit (HPC Type A)

Figure 1. Drug released, after pre-exposure 2 hours to 0.1 M HCl and 30 minutes in buffer pH 6.8, from tablets containing HPC Type A and HPC Type B in the separating layer of enteric coated pellets (according to Example 2).

Fig. 2

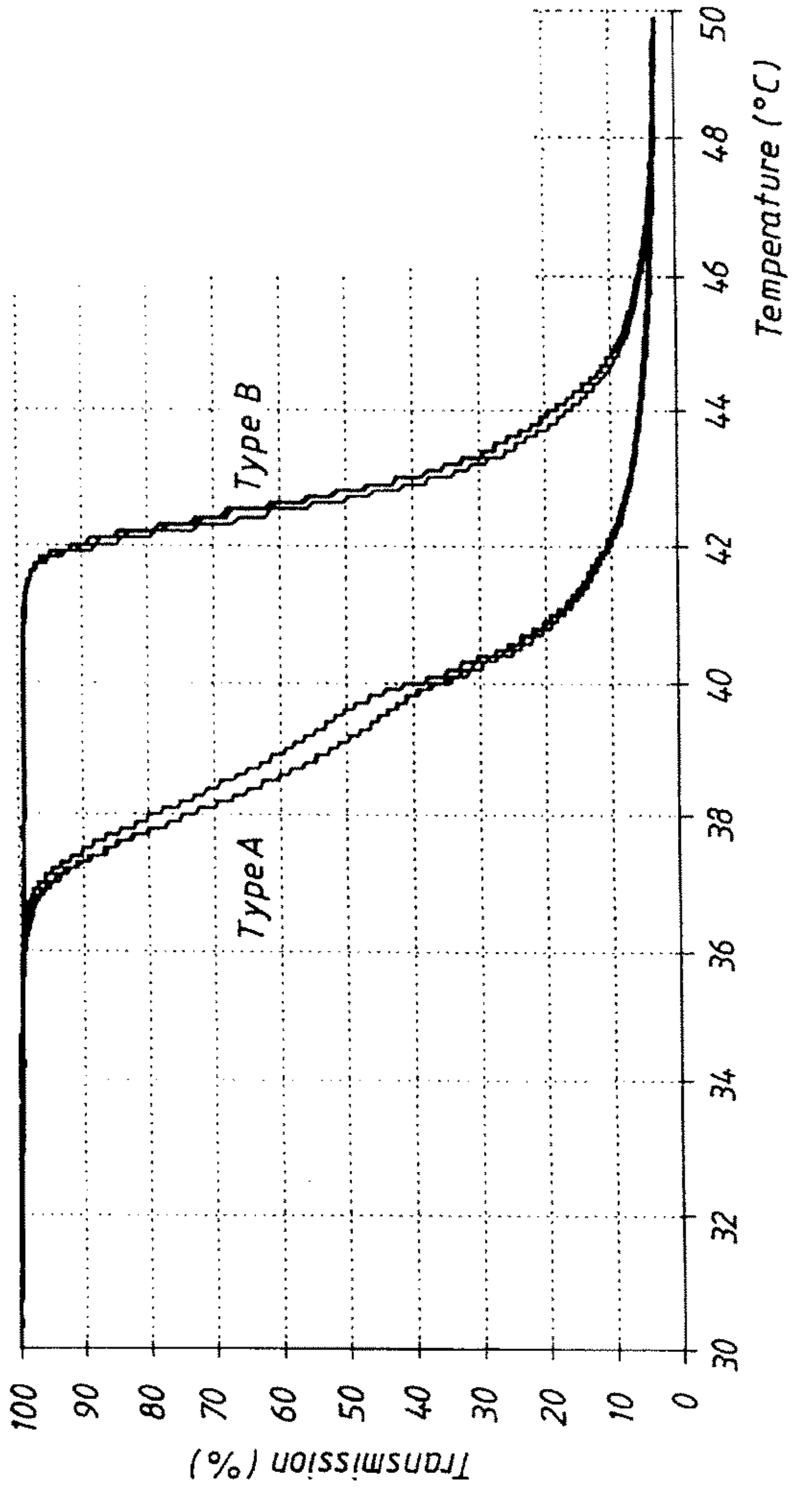

Type A
Type B
Temperature (°C)
Transmission (%)
30
32
34
36
38
40
42
44
46
48
50
100
90
80
70
60
50
40
30
20
10
0

Figure 2. Cloud point determinations of the two different qualities of HPC named Type A and Type B (according to Example 3).

Fig. 3a

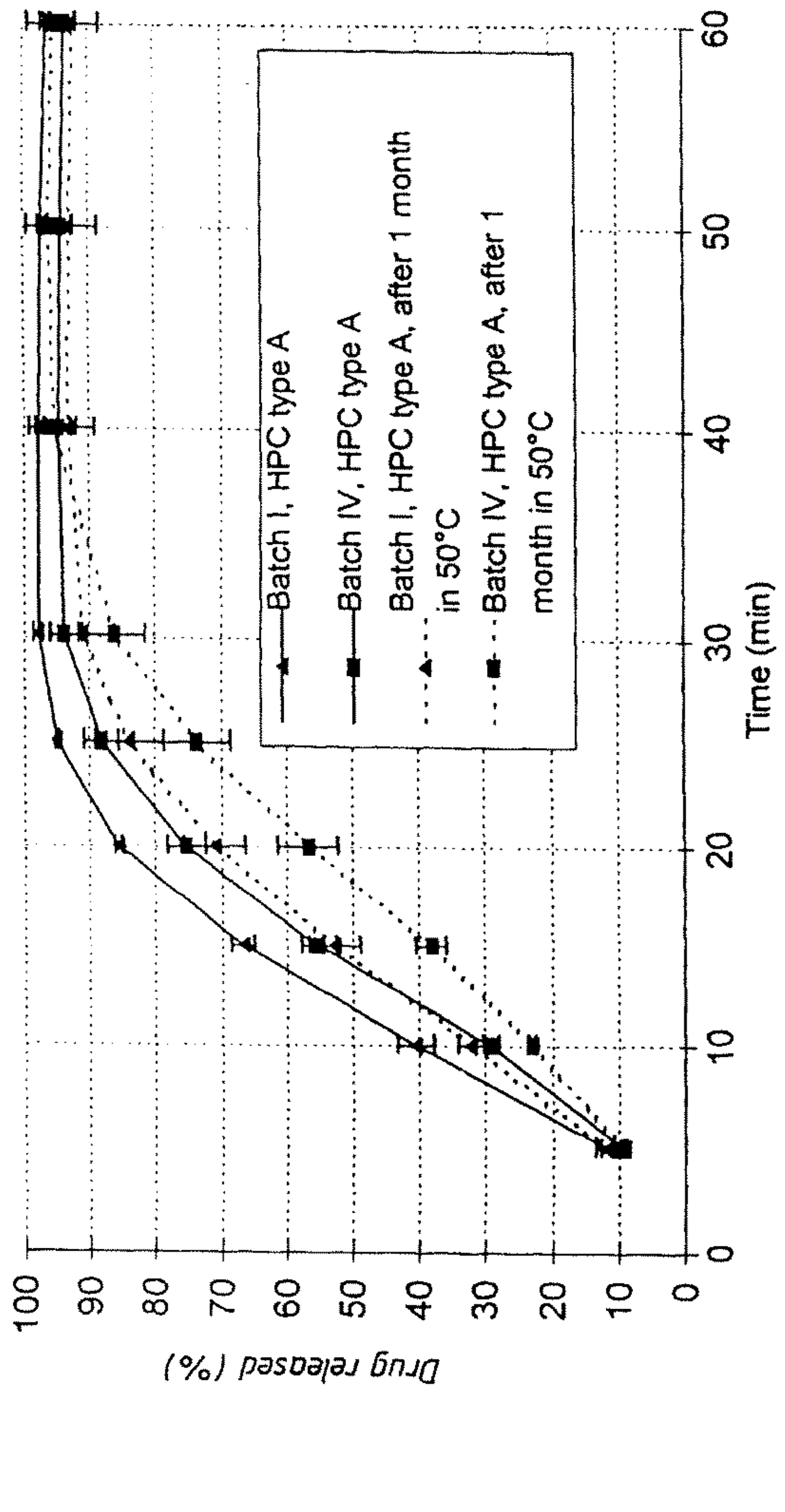

Drug released (%)
Time (min)
Batch I, HPC type A
Batch IV, HPC type A
Batch I, HPC type A, after 1 month in 50°C
Batch IV, HPC type A, after 1 month in 50°C
0
10
20
30
40
50
60
70
80
90
100

Figure 3a). Release of omeprazole from formulations containing HPC type A (according to Example 1) in separating layer of enteric coated pellets, before and after storage.

Fig.3b

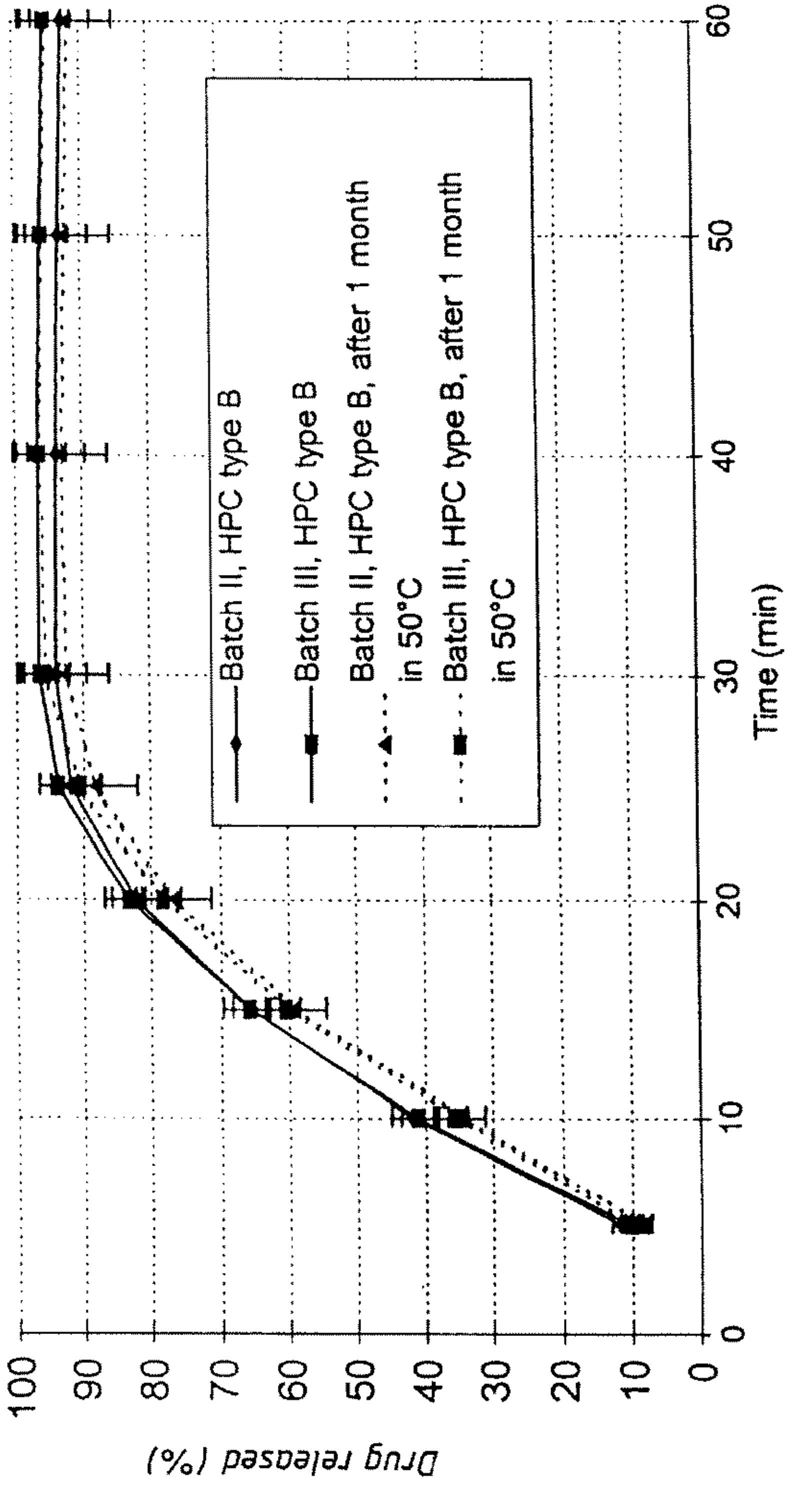

Drug released (%)
100
90
80
70
60
50
40
30
20
10
0
Time (min)
0
10
20
30
40
50
60
Batch II, HPC type B
Batch III, HPC type B
Batch II, HPC type B, after 1 month in 50°C
Batch III, HPC type B, after 1 month in 50°C

Figure 3b). Release of omeprazole from formulations containing HPC type B (according to Example 1) in separating layer of enteric coated pellets, before and after storage.

PHARMACEUTICAL FORMULATION COMPRISING OMEPRAZOLE

FIELD OF THE INVENTION

The present invention relates to an oral pharmaceutical formulation comprising the acid labile H^+, K^+-ATPase inhibitor omeprazole, an alkaline salt of omeprazole, one of the single enantiomers thereof or an alkaline salt of one of the single enantiomers of omeprazole. In the following these compounds are referred to as omeprazole. The formulation is in the form of a multiple unit dosage form that comprises enteric coating layered units of omeprazole. More specifically, the units comprise a core material that comprises omeprazole optionally in admixture with an alkaline reacting substance, and in admixture with one or more pharmaceutically acceptable excipients such as a binding agent, a filling agent and/or a disintegrating agent. Furthermore, each unit comprises a separating layer to separate the enteric coating layer from the core material. The separating layer comprises a specific quality of hydroxypropyl cellulose (HPC), and optionally pharmaceutical excipients. More specifically, the HPC quality is defined by having a specific cloud point.

Furthermore, the present invention refers to the use of the specific quality of HPC in the manufacture of a pharmaceutical formulation comprising omeprazole, and the use of such a pharmaceutical formulation in medicine.

BACKGROUND OF THE INVENTION

Omeprazole, an alkaline salt thereof, the single enantiomers of omeprazole and an alkaline salt of the single enantiomers of omeprazole, all compounds hereinafter referred to as omeprazole, are used in the treatment of gastric acid related diseases. Omeprazole and pharmaceutically acceptable salts thereof are described in EP 5129, and some specific alkaline salts of omeprazole are described in EP 124 495 and W095/01977. Certain salts of the single enantiomers of omeprazole and their preparations are described in WO94/27988.

Omeprazole is generally known to be useful for inhibiting gastric acid secretion in mammals and man by controlling gastric acid secretion at the final step of the acid secretory pathway. Thus, in a more general sense, it may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcers and duodenal ulcers. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with non ulcer dyspepsia, in patients with symptomatic gastro-oesophageal reflux disease, and in patients with gastrinomas. It may also be used in a patient in intensive care situations, in a patient with acute upper gastrointestinal bleeding, pre-and post-operatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, it may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these, as well as in the treatment or prophylaxis of inflammatory conditions in mammals, including man.

Omeprazole is, however, susceptible to degradation or transformation in acidic and neutral media. The degradation is catalyzed by acidic compounds and is stabilized in mixtures with alkaline compounds. The chemical stability of omeprazole is also affected by moisture, heat, and organic solvents and to some degree by light.

Due to the chemical stability properties of omeprazole, it is obvious that an oral solid dosage form comprising omeprazole must be protected from contact with the acidic gastric juice. Omeprazole must also be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur.

A pharmaceutical oral dosage form of omeprazole is best protected from contact with acidic gastric juice by an enteric coating layer. For instance, EP 247 983 describes enteric coated formulations of omeprazole. Such as formulation contains omeprazole in the form of a core unit containing omeprazole together with an alkaline salt or containing an alkaline salt of omeprazole optionally together with an alkaline salt, the core unit is layered with a separating layer and an enteric coating layer. In WO 96/01623 a multiple unit tableted dosage formulation comprising omeprazole is described.

The oral formulations described in EP 247 983 and the tablet formulations described in WO 96/01623 are examples of enteric coating layered formulations that comprise or optionally comprise a separating layer to separate the acidic enteric coating material from omeprazole being an acid susceptible substance. HPC may be used in a layer that separates the core material from the enteric coating layer in the described formulations. All ingredients, including HPC qualities, used in a pharmaceutical preparation must fulfil strict criteria, such as for instance requirements defined in pharmacopoeial monographs.

The rate of release of omeprazole from a pharmaceutical dosage form can influence the total extent of absorption of omeprazole into the general circulation (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113–120). Therefore the limits for rate of release of the omeprazole from the pharmaceutical formulation are stated in the marketing approval for the products. The release of omeprazole is affected both by the chemical stability of the active substance and the release stability of the pharmaceutical formulation. If the formulation is unstable with respect to the release rate, the drug will have a non-accepted storage time, i.e. the expiration period for the product will be too short.

It has now surprisingly been found that different batches of HPC, which fulfil all pharmacopoeial requirements, used as material for the separating layer in a pharmaceutical formulation comprising omeprazole, may result in different release rate over time. Thus, the storage period for the pharmaceutical formulation may not be acceptable. One parameter of interest for the HPC's influence on the release stability is its water solubility.

The aqueous solubility of HPC decreases with increasing temperature due to polymer phase separation. This is observed as a clouding of the polymer solution when the temperature is increased. Cloud point is the temperature at which this polymer phase separation occurs. Cloud point is determined by measuring the light transmission through the polymer solution. The light transmission of a specific system where the polymer is dissolved, that is a transparent polymer solution without clouding, is defined as light transmission 100%. In this patent application cloud point is defined as the temperature where the light transmission of a specific system is 96% when a commercial instrument from Mettler is used. For other cloud point systems and instruments another light transmisson may be specified for each system.

One problem that can be avoided by the new formulation and use of a specific quality of HPC, is that the storage period for the dosage form can be extended and guarantied. From an economical aspect it is advantageous to specify and check the HPC quality thereby keeping a long expire date of the dosage form.

OUTLINE OF THE INVENTION

It has now been found that a quality of HPC with a cloud point of not less than 38° C. determined as the temperature where the light transmission of a specified system is 96% measured by a Mettler FP90/FP 81C instrument is desirable in an enteric coating layered pharmaceutical formulation comprising omeprazole. Preferably, the HPC should have a cloud point of not less than 40° C., and more preferably not less than 41° C. When another instrument is used for determination, the cloud point may be specified in other terms. An upper limit for the cloud point is not critical and therefore there is no need to specify that.

The HPC is used as a constituent of a separating layer separating the core material comprising omeprazole from the enteric coating layer. The HPC quality defined in the present patent application is desirable in fulfilling the criteria on release rate stability and to be suitable for oral administration forms comprising omeprazole.

DETAILED DESCRIPTION OF THE DRAWINGS

FIG. 1 shows two graphs representing two different dosage forms based on two qualities of HPC named Type A and Type B. The graphs show released omeprazole from the dosage forms after 3 months and 6 months storage at accelerated conditions at 40° C. and 75% relative humidity. The two HPC qualities are used as a constituent of the separating layer described in Example 2 below. With a separating layer comprising HPC Type A the release rate of omeprazole over time has decreased. With the HPC Type B the release rate of omeprazole over time is almost the same as for a freshly produced product.

FIG. 2 shows two graphs representing two different qualities of HPC named Type A and Type B. The graphs show cloud point determinations for the two HPC qualities used as a constituent of the separating layer described in Examples 1–3 below.

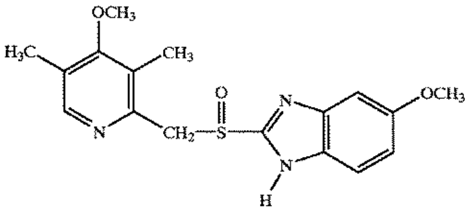
FIG. 3*a*) and FIG. 3*b*) show graphs representing two different dosage forms based on two qualities of HPC named Type A and Type B. FIG. 3*a*) shows released omeprazole from dosage forms comprising HPC type A, i.e. a reference. FIG. 3*b*) shows released omeprazole from dosage forms comprising HPC type B, i.e. according to the invention. The two HPC qualities are used as a constituent of the separating layer described in Example 1 below.

DETAILED DESCRIPTION OF THE INVENTION

Core Materials.

Omeprazole with formula Ia, is preferably formulated into an oral composition in the form of a pharmaceutically acceptable salt, such as an alkaline salt selected from the group of the Mg^{2+}, Ca^{2+}, Na^{+} and K^{+} salts, more preferably the Mg salt. Omeprazole may also be used in the form of one of the single enantiomers of omeprazole or an alkaline salt of one of the single enantiomers of omeprazole, especially an alkaline salt of the (–)-enantiomer of omeprazole, and more preferably the Mg^{2+} salt of the (–)-enantiomer of omeprazole.

(Ia)



The core material for the individually enteric coating layered pellets can be composed and formulated according to different principles, such as described in EP 247 983 and WO 96/01623 hereby incorporated by reference. For instance, omeprazole is mixed with one or more pharmaceutical constituents to obtain preferred handling and processing properties and also to obtain a suitable concentration of omeprazole in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives, can be used.

Preferably, omeprazole, optionally after mixing with an alkaline compound, is mixed with suitable constituents including a binding agent and formulated into a core material. Said core materials may be produced by extrusion/spheronization, balling or compression and by utilizing different process equipment. The formulated core materials may have a size of less than approximately 2 mm. The manufactured core materials can be layered further with additional ingredients, optionally comprising active substance, and/or be used for further processing.

Alternatively, inert seeds layered with active substance (the active substance is optionally mixed with alkaline compounds) can be used as the core material for the further processing. The seeds, which are to be layered with the active substance, can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures.

Before the seeds are layered, for instance by using granulating or spray coating/layering equipment, omeprazole is mixed with a binding agent and optionally further components. Such further components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures.

The binders are for example celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, microcrystalline cellulose and carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants, such as for instance sodium lauryl sulphate.

The active substance may also be mixed with an alkaline pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate co-precipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $Mg_6Al_2(OH)_{16}CO_3.4H_2O$,

$MgO.Al_2O_3$. $2SiO_2.nH_2O$ or similar compounds; organic ph-buffering substances such as trihydroxy methyl amino methane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

Separating Layer(s)

The core material containing omeprazole must, according to EP 247 983, be separated from the enteric coating polymer(s) containing free carboxyl groups, which may otherwise cause degradation/discolouration of omeprazole during the coating process or during storage.

According to the present invention, the separating layer comprises a specific quality of HPC. This specific quality of HPC should preferably have a cloud point of at least 38° C. determined by a Mettler instrument. The cloud point is determined in a mixed disodium hydrogenphosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3. The mixed solution used for the cloud point determination has a pH of 6.75–6.85. The concentration of HPC in the mixed solution is 1.0% (w/w) for the Mettler instrument. For more detailed information on the composition of the mixed solution, see below in the experimental section. Preferably, the HPC has a low viscosity, such as for instance below 400 mpas in a 5% (w/w) water solution at 25° C.

Alternatively, the quality of HPC may be determined by a method that correlates with the method described above, e.g. NIR spectrophotometry.

Additives such as plasticizers, colorants, pigments, fillers, anti-tacking, buffering agents, and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc, and other additives may also be included in the separating layer(s).

Enteric Coating Layer(s)

One or more enteric coating layers are applied onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in a suitable organic solvent. As enteric coating layer polymers one or more, separately or in combination, of the following polymers can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s). For environmental reasons, an aqueous coating process may be preferred. In such aqueous processes methacrylic acid copolymers are most preferred.

The enteric coating layers may contain pharmaceutically acceptable plasticizers to obtain desirable mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers. The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s). Additives such as dispersants, colorants, pigments, polymers e.g. poly(ethylacrylate, methylmethacrylate), anti-tacking and anti-foaming agents may also be included in the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acidic susceptible active substance.

To protect the acidic susceptible active substance, the enteric coating layer(s) preferably constitute(s) a thickness of at least approximately 10 μm. The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

The pellets or units covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipment such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the layering process.

Final Dosage Form.

The prepared pellets may be filled in hard gelatine capsules or compressed with suitable tablet excipients into a tableted multiple unit formulation, and the latter is preferred. Final dosage forms may also include but is not restricted to effervescent tablets, and combinations of omeprazole with other active ingredients, such as for instance antibacterial substances, NSAID(s), motility stimulating agents or antacids.

Experimental Section.

EXAMPLE 1

Test of Omeprazole Multiple Unit Tablets, in which the Pellets are Layered with Different Types of HPC Used as a Constituent of the Separation Layer (Laboratory Scale).

Omeprazole tablets with the following composition were prepared according to the description in WO 96/01623. Sugar spheres were spray layered in a fluidized bed with an aqueous suspension of omeprazole magnesium salt and HPMC. The prepared pellets were layered with a separating layer and thereafter enteric coated. Enteric coated pellets were mixed with tablets excipients and compressed into a multiple unit tablet.

The composition of the tested omeprazole tablets (20 mg strenght) was as follows.

NAME OF INGREDIENT	FORMULA (mg/tablet)
Omeprazole magnesium	20.6
Glyceryl monostearate	1.4
Hydroxypropylcellulose	4.8
Hydroxypropyl metylcellulose	4.6
Magnesium stearate	0.7
Methacrylic acid copolymer type C	27
Microcrystalline cellulose	220
Polysorbate 89	0.1
Polyvinylpyrrolidone crosslinked	4.6
Sodium stearyl fumarate	0.5
Sugar spheres	22
Talc	8.3
Triethyl citrate	8.2

Omeprazole multiple unit tablets prepared with a separating layer on the pellets which separating layer comprises HPC, of either quality i.e type A or type B. HPC of the two types fulfill all requirements in the PhEur as well as the USP. However, the HPC of the two types differ with respect to some physical/chemical characteristics, e.g. cloud point.

The prepared tablets were tested according to the description below. The tablets, i.e. the pellets, were prepared from the same batch of omeprazole magnesium, and with the same enteric coating material. The release of omeprazole was tested on stored tablets after 0 month, and 6 months storage. The amount of released omeprazole within 30 minutes in a buffer solution was determined.

The tablets were pre-exposed to hydrochloric acid at 37° C. for 2 hours. Thereafter the drug release in buffer solution pH 6.8 at 30 minutes was determined by liquid chromatography. The buffer solution pH 6.8 was a mixture of disodium hydrogenphosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3, pH should be between 6.75 and 6.85. The hydrochloric acid 0.1 M was prepared by dissolving 213 ml of conc. HCl in water and added with water to 25 000 ml. The disodium hydrogen phosphate solution 0.086 M was prepared by dissolving 382 g $Na_2HPO_4.2H_2O$ in water and dilute to 25 000 ml with water.

The stability testing was performed on (20 mg strength) tablets packed in plastic bottles with desiccant (the tablets were not covered by a tablet coat).

Results are shown in FIG. **3***a*) and FIG. **3***b*). FIG. **3***a*) shows results with the HPC quality type A, i.e. a reference, and FIG. **3***b*) shows results with HPC type B, i.e. according to the instant invention.

EXAMPLE 2

Release of Omeprazole from Tablets Comprising Different Types of HPC as a Constituent of the Separating Layer

Pilot scale batches (using HPC of type A: 6 batches, and type B: 2 batches) were manufactured in order to confirm the improvement found during the laboratory testing in Example 1. Results from stability studies are shown in FIG. **1**.

The comparison clearly indicates improved release rate stability for tablets containing HPC of type B relative to that of type A.

General compositions for omeprazole tablets (20 mg strength):

NAME OF INGREDIENT	FORMULA (mg/tablet)
Omeprazole magnesium	20.6
Colour iron oxide reddish-brown	0.3
Glyceryl monostearate	1.4
Hydroxypropylcellulose	4.8
Hydroxypropyl metylcellulose	15
Magnesium stearate	0.7
Methacrylic acid copolymer type C	27
Microcrystalline cellulose	220
Paraffin	0.2
Polyethylene glycol 6000	2.5
Polysorbate 80	0.1
Polyvinylpyrrolidone crosslinked	4.6
Sodium stearyl fumarate	0.5
Sugar spheres	22
Talc	8.3
Titanium dioxide	2.2
Triethyl citrate	8.2

The tablets were manufactured as described in example 1, with the additional step of a tablet coat comprising HPMC, PEG 6 000, and pigment.

EXAMPLE 3

Cloud Point Determinations

Omeprazole tablets were manufactured in laboratory scale as described in example 1.

Cloud point determinations of the HPC types in the Mettler instrument was conducted in the following way. The cloud point of the HPC types was determined in a mixed phosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3. The mixed solution used for the cloud point determination had a pH of 6.75–6.85. The concentration of HPC in the mixed solution was 1.0% (w/w). It is essential for the specificity of the cloud point determination that this system is used in the chosen instrument. The Mettler instrument comprises the following parts: Mettler FP90 Central processor, FP81C Measuring unit and ME-18572 boiling point tubes. A temperature range of 30.0 to 50.0° C. was used and a heating rate of 1.0° C./min. The cloud point is defined as the temperature where the light transmission is 96%.

The results are shown in FIG. **2**.

What is claimed is:

1. An enteric coated oral pharmaceutical formulation comprising:

(a) a core material which comprises an active ingredient selected from the group consisting of omeprazole, an alkaline salt of omeprazole, one of the single enantiomers of omeprazole and an alkaline salt of one of the single enantiomers of omeprazole;

(b) a separating layer; and

(c) an enteric coating layer,

wherein the separating layer comprises a hydroxypropyl cellulose (HPC) with a cloud point of at least 38° C., and

wherein the light transmission at cloud point of a system comprising the HPC dissolved in a concentration of 1.0% (w/w) in a mixed solution of disodium hydrogen phosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3 at a pH of 6.75–6.85 is 96%.

2. The formulation according to claim **1**, wherein the HPC has a cloud point of at least 40° C.

3. The formulation according to clam **1**, wherein the HPC has a cloud point of at least 41° C.

4. The formulation according to claim **1**, wherein the enteric coating layer comprises a methacrylic acid copolymer.

5. The formulation according to claim **1**, wherein the HPC has a low viscosity.

6. The formulation according to claim **1**, wherein the active ingredient is omeprazole.

7. The formulation according to claim **1**, wherein the active ingredient is a magnesium salt of omeprazole.

8. The formulation according to claim **1**, wherein the active ingredient is a magnesium salt of the (−)-enantiomer of omeprazole.

9. The formulation according to claim **1**, wherein the core material further comprises an alkaline reacting compound.

10. The formulation according to claim **1** or **9**, wherein the core material further comprises a pharmaceutically acceptable excipient selected from the group consisting of binding agents, fillers, lubricants, disintegrating agents, surfactants and mixtures thereof.

11. A method for the treatment of gastrointestinal diseases in mammals comprising administering to a host in need thereof a therapeutically effective amount of the pharmaceutical formulation according to any one of claims **2**–**8** or **1**.

12. A process for the manufacture of an enteric coated oral pharmaceutical formulation according to claim **1**, comprising the steps:

(a) forming the core material comprising the active ingredient;

(b) applying the separating layer onto the core; and

(c) applying the enteric coating layer onto the core coated with the separating layer.

13. The process according to claim **12**, wherein an alkaline reacting compound is mixed with the active ingredient to form the core material.

14. The process according to claim **12** or **13**, wherein a pharmaceutically acceptable excipient selected from the group consisting of binding agents, fillers, lubricants, disintegrating agents, surfactants and mixtures thereof is added to form the core material.

15. The process according to claim **12**, wherein an alkaline reacting compound is mixed with the active ingredient and a binding agent to form the core material.

16. The process according to claim **12**, wherein the HPC has a cloud point of at least 40° C.

17. The process according to claim **12**, wherein the HPC has a cloud point of at least 41° C.

18. The process according to claim **12**, wherein the enteric coating layer comprises a methacrylic acid copolymer.

19. The process according to claim **12**, wherein the HPC has a low viscosity.

20. The process according to claim **12**, wherein the active ingredient is omeprazole.

21. The process according to claim **12**, wherein the active ingredient is a magnesium salt of omeprazole.

22. The process according to claim **12**, wherein the active ingredient is a magnesium salt of the (–)-enantiomer of omeprazole.

* * * * *